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=> d his ful

     (FILE 'HOME' ENTERED AT 10:04:56 ON 18 OCT 2005)

     FILE 'REGISTRY' ENTERED AT 10:05:10 ON 18 OCT 2005
L1             4 SEA ABB=ON  (68047-06-3 OR 82413-20-5 OR 84449-90-1 OR
                  10540-29-1 OR 68047-06-3)/RN
L2             7 SEA ABB=ON  (180915-84-8 OR 180915-78-0 OR 180916-16-9 OR
                  193274-89-4 OR 180916-14-7 OR 180915-86-0 OR 180916-15-8)/RN
L3             4 SEA ABB=ON  (PGD1 OR PGD2 OR PGE2 OR PGE1 OR PGF2 OR PGF2A)/CN
                  E PGF2A/CN
                  E PGF2A/CN
L4             1 SEA ABB=ON  PGF2A/CN
L5             5 SEA ABB=ON  L3 OR L4
L6             6 SEA ABB=ON  L5 OR 195962-24-4/RN

     FILE 'HCAPLUS' ENTERED AT 10:09:46 ON 18 OCT 2005
L7         10946 SEA ABB=ON  L1 OR ?DROLOXIFENE? OR ?RALOXIFENE? OR ?TAMOXIFEN?

L8            10 SEA ABB=ON  L7(5A)(L3 OR L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1 OR
                  PGF2 OR PGF2A OR PGF2A)
L9            13 SEA ABB=ON  L7(10A)(L3 OR L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1
                  OR PGF2 OR PGF2A OR PGF2A)
L10           15 SEA ABB=ON  L7(20A)(L3 OR L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1
                  OR PGF2 OR PGF2A OR PGF2A)
L11            3 SEA ABB=ON  L10 AND (?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?)
                  OR ?OSTEOPOROS? OR ?PAGET?)
L12           15 SEA ABB=ON  L10 OR L11
L13            6 SEA ABB=ON  L12 AND (PRD<19960228 OR PD<19960228)

     FILE 'REGISTRY' ENTERED AT 10:15:40 ON 18 OCT 2005
L14           11 SEA ABB=ON  L1 OR L2

     FILE 'HCAPLUS' ENTERED AT 10:15:51 ON 18 OCT 2005
L15        10991 SEA ABB=ON  L14 OR ?DROLOXIFENE? OR ?RALOXIFENE? OR ?TAMOXIFEN?
L16           10 SEA ABB=ON  L15(5A)(L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1 OR PGF2
                  OR PGF2A OR PGF2A)
L17           15 SEA ABB=ON  L15(20A)(L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1 OR
                  PGF2 OR PGF2A OR PGF2A)
L18            3 SEA ABB=ON  L17 AND (?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?)
                  OR ?OSTEOPOROS? OR ?PAGET?)
L19           15 SEA ABB=ON  L17 OR L18
L20            6 SEA ABB=ON  L12 AND (PRD<19960228 OR PD<19960228)
L21          786 SEA ABB=ON  L15 AND (?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?)
                  OR ?OSTEOPOROS? OR ?PAGET?)
L22           96 SEA ABB=ON  L21 AND (PRD<19960228 OR PD<19960228)
L23        48257 SEA ABB=ON  (L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1 OR PGF2 OR
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L24          690 SEA ABB=ON  L23 AND (?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?)
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L25          406 SEA ABB=ON  L24 AND (PRD<19960228 OR PD<19960228)
L26            1 SEA ABB=ON  L17(20A)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?)
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L27          295 SEA ABB=ON  L15(5A)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?) OR
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L28          239 SEA ABB=ON  L15(3A)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?) OR
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L29           37 SEA ABB=ON  L28 AND (PRD<19960228 OR PD<19960228)
L30          236 SEA ABB=ON  L23(3A)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?) OR
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L31         211 SEA ABB=ON  L23(2A)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?) OR
                ?OSTEOPOROS? OR ?PAGET?)
L32         190 SEA ABB=ON  L23(3W)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?) OR
                ?OSTEOPOROS? OR ?PAGET?)
L33         149 SEA ABB=ON  L32 AND (PRD<19960228 OR PD<19960228)
L34         165 SEA ABB=ON  L23(2W)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?) OR
                ?OSTEOPOROS? OR ?PAGET?)
L35         134 SEA ABB=ON  L34 AND (PRD<19960228 OR PD<19960228)
L36          14 SEA ABB=ON  L23(2W)(?BONE?(W)?LOSS? OR ?OSTEOPOROS? OR
                ?PAGET?)
L37         165 SEA ABB=ON  L23(2W)(?BONE?(W)(?LOSS? OR ?RESORP?) OR ?OSTEOPORO
                S? OR ?PAGET?)
L38          21 SEA ABB=ON  L23(2A)(?BONE?(W)?LOSS? OR ?OSTEOPOROS? OR
                ?PAGET?)
L39          29 SEA ABB=ON  L23(4A)(?BONE?(W)?LOSS? OR ?OSTEOPOROS? OR
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L40         249 SEA ABB=ON  L23(4A)(?BONE?(W)(?LOSS? OR ?RESORP?) OR ?OSTEOPORO
                S? OR ?PAGET?)
L41         211 SEA ABB=ON  L23(2A)(?BONE?(W)(?LOSS? OR ?RESORP?) OR ?OSTEOPORO
                S? OR ?PAGET?)
L42         190 SEA ABB=ON  L23(3W)(?BONE?(W)(?LOSS? OR ?RESORP?) OR ?OSTEOPORO
                S? OR ?PAGET?)
L43         149 SEA ABB=ON  L42 AND (PRD<19960228 OR PD<19960228)
L44           9 SEA ABB=ON  L36 AND (PRD<19960228 OR PD<19960228)
L45          52 SEA ABB=ON  L20 OR L29 OR L44  52 cits from CA Rlse

    FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 10:31:33 ON
    18 OCT 2005
L46          42 SEA ABB=ON  L45
L47          26 DUP REMOV L46 (16 DUPLICATES REMOVED)  26 cits from above dbs

    FILE 'USPATFULL' ENTERED AT 10:35:12 ON 18 OCT 2005
L48           8 SEA ABB=ON  L20 OR L29 OR L44  8 cits from USPatFull

    FILE 'HCAPLUS' ENTERED AT 10:36:00 ON 18 OCT 2005
              SAV L20 LEI051L20/A
              SAV L29 LEI051L29/A  ) saved

    FILE HOME

    FILE REGISTRY
    Property values tagged with IC are from the ZIC/VINITI data file
    provided by InfoChem.

    STRUCTURE FILE UPDATES:   17 OCT 2005  HIGHEST RN 865410-76-0
    DICTIONARY FILE UPDATES:  17 OCT 2005  HIGHEST RN 865410-76-0

    New CAS Information Use Policies, enter HELP USAGETERMS for details.

    TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

      Please note that search-term pricing does apply when
      conducting SmartSELECT searches.

    ******************************************************************
    *                                                                *
    * The CA roles and document type information have been removed from *
    * the IDE default display format and the ED field has been added,  *
    * effective March 20, 2005.  A new display format, IDERL, is now   *
    * available and contains the CA role and document type information. *
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* *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE HCAPLUS

FILE COVERS 1907 - 18 Oct 2005 VOL 143 ISS 17
FILE LAST UPDATED: 17 Oct 2005 (20051017/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 15 OCT 2005 (20051015/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 12 October 2005 (20051012/ED)

FILE RELOADED: 19 October 2003.

FILE EMBASE
FILE COVERS 1974 TO 13 Oct 2005 (20051013/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE JAPIO
FILE LAST UPDATED: 4 OCT 2005 <20051004/UP>
FILE COVERS APR 1973 TO JUNE 30, 2005

<<< GRAPHIC IMAGES AVAILABLE >>>

FILE JICST-EPLUS
FILE COVERS 1985 TO 17 OCT 2005 (20051017/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 13 Oct 2005 (20051013/PD)
FILE LAST UPDATED: 13 Oct 2005 (20051013/ED)
HIGHEST GRANTED PATENT NUMBER: US6954941
HIGHEST APPLICATION PUBLICATION NUMBER: US2005229280
CA INDEXING IS CURRENT THROUGH 13 Oct 2005 (20051013/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 13 Oct 2005 (20051013/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

L15	10991	SEA FILE=HCAPLUS ABB=ON L14 OR ?DROLOXIFENE? OR ?RALOXIFENE? OR ?TAMOXIFEN?
L20	6	SEA FILE=HCAPLUS ABB=ON L12 AND (PRD<19960228 OR PD<19960228)
L23	48257	SEA FILE=HCAPLUS ABB=ON (L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1 OR PGF2 OR PGF2A OR PGF2A)
L28	239	SEA FILE=HCAPLUS ABB=ON L15(3A)(?BONE?(W)(?LOSS? OR ?RESORP? OR ?LOSE?) OR ?OSTEOPOROS? OR ?PAGET?)
L29	37	SEA FILE=HCAPLUS ABB=ON L28 AND (PRD<19960228 OR PD<19960228)
L36	14	SEA FILE=HCAPLUS ABB=ON L23(2W)(?BONE?(W)?LOSS? OR ?OSTEOPOROS? OR ?PAGET?)
L44	9	SEA FILE=HCAPLUS ABB=ON L36 AND (PRD<19960228 OR PD<19960228)
L45	52	SEA FILE=HCAPLUS ABB=ON L20 OR L29 OR L44

=> d ibib abs l45 1-52

L45 ANSWER 1 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:171204 HCAPLUS
DOCUMENT NUMBER: 126:210851
TITLE: Altered uterine sensitivity to oxytocin and prostaglandin F2α in dimethylbenz(a)anthracene (DMBA)-induced rat mammary carcinoma: the effects of tamoxifen and/or recombinant human interferon α2b therapy
AUTHOR(S): Badary, Osama A.; Agha, Azza M.; El-Sayed, El-Sayed M.; Hamada, Farid M. A.
CORPORATE SOURCE: Pharmacology Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
SOURCE: Pharmacological Research (1996), 34(3/4), 99-103
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study aimed to investigate the long-term toxicity of a preventive regimen of tamoxifen (TAM) and recombinant human interferon alpha 2b (rHuIFN α2b) on the uterine responsiveness of tumor-bearing rats. The exptl. tumor was induced by dimethylbenz(a)anthracene (DMBA) in virgin female albino rats and the therapy was started two months after carcinogen administration. The acute effect of DMBA on the uterine sensitivity was also assessed 24 h post-carcinogen. The uterotonic potentials of oxytocin and prostaglandin F2α (PGF2α) were markedly reduced in the control tumor-bearing group as compared to the normal one. Similarly, acute DMBA administration showed reduced uterine sensitivity to both agents. Treatment with either TAM or combined TAM/rHuIFN α2b did not affect the uterine response to either oxytocin or PGF2α, while rHuIFN α2b increased the uterine sensitivity to oxytocin but not to PGF2α. These data indicate that the carcinogenic agent per se and the presence of tumor reduce the contractile response in the rat uterus to oxytocic agents. Moreover, combined TAM/rHuIFN α2b does not markedly affect the uterine sensitivity in DMBA-induced mammary carcinoma-bearing rats.

L45 ANSWER 2 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:85113 HCAPLUS
DOCUMENT NUMBER: 126:99321
TITLE: Methods for minimizing bone loss effects of anabolic agents by hydroxyphenylbenzothiophene derivatives
INVENTOR(S): Cullinan, George Joseph; Fontana, Steven Anthony
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 747054	A2	19961211	EP 1996-304180	19960606 <--
EP 747054	A3	19970305		
EP 747054	B1	20020821		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5599822	A	19970204	US 1995-467475	19950606

CA 2223055	AA	19961212	CA 1996-2223055		19960605 <--
WO 9639138	A1	19961212	WO 1996-US8875		19960605 <--
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RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9660430	A1	19961224	AU 1996-60430		19960605 <--
AU 696209	B2	19980903			
CN 1192145	A	19980902	CN 1996-195975		19960605 <--
BR 9608389	A	19990504	BR 1996-8389		19960605 <--
JP 11507051	T2	19990622	JP 1997-501343		19960605 <--
ZA 9604778	A	19971208	ZA 1996-4778		19960606 <--
IL 118590	A1	19991028	IL 1996-118590		19960606 <--
ES 2181849	T3	20030301	ES 1996-304180		19960606 <--
NO 9705581	A	19971203	NO 1997-5581		19971203 <--
PRIORITY APPLN. INFO.:			US 1995-467475	A	19950606 <--
			WO 1996-US8875	W	19960605

OTHER SOURCE(S): MARPAT 126:99321

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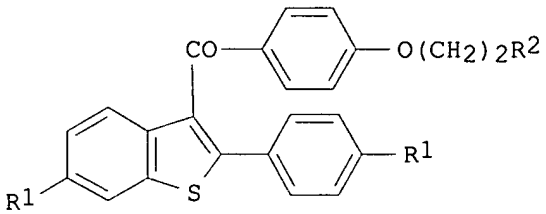

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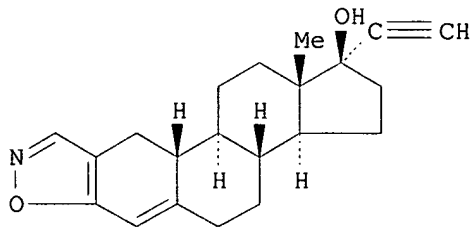

II

AB Method for minimizing the bone loss effect of I or a pharmaceutically acceptable salt thereof comprises concurrently or sequentially administering an effective amount of a compound of I [R1 = H, OH, O(C1-C4 alkyl), OCOC6H5, OCO(C1-C6 alkyl), or OSO2(C4-C6 alkyl); R2 = 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino] or a pharmaceutically acceptable salt thereof. Also provided is a method for minimizing bone loss induced by the administration of a formula II compound comprising concurrently or sequentially administering a bone anabolic agent. A pharmaceutical capsule contained raloxifene.HCl 50, starch 150, starch flowable powder 397, and silicone fluid 350 cSt 3.0 mg.

L45 ANSWER 3 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:85111 HCAPLUS
DOCUMENT NUMBER: 126:99320
TITLE: Methods for minimizing bone loss effects of antiestrogen compounds by 6-hydroxyl-2-(4-hydroxyphenyl)benzo[b]thiophene derivatives
INVENTOR(S): Cullinan, George Joseph; Fontana, Steven Anthony; Fuchs-Young, Robin Sharon Lee; Glasebrook, Andrew Lawrence
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
EP 747056	A2	19961211	EP 1996-303874		19960530	<--
EP 747056	A3	19970305				
EP 747056	B1	19991215				
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE						
AT 187643	E	20000115	AT 1996-303874		19960530	<--
ES 2142545	T3	20000416	ES 1996-303874		19960530	<--
PT 747056	T	20000531	PT 1996-303874		19960530	<--
CA 2223174	AA	19961212	CA 1996-2223174		19960605	<--
WO 9639141	A1	19961212	WO 1996-US8810		19960605	<--
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RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG						
AU 9659816	A1	19961224	AU 1996-59816		19960605	<--
AU 696927	B2	19980924				
ZA 9604681	A	19971205	ZA 1996-4681		19960605	<--
BR 9608390	A	19990504	BR 1996-8390		19960605	<--
CN 1239429	A	19991222	CN 1996-195984		19960605	<--
IL 118573	A1	20000131	IL 1996-118573		19960605	<--
JP 2001501907	T2	20010213	JP 1997-501298		19960605	<--
NO 9705560	A	19980126	NO 1997-5560		19971202	<--
GR 3032863	T3	20000731	GR 2000-400555		20000303	<--
PRIORITY APPLN. INFO.:			US 1995-471111	A	19950606	<--
			WO 1996-US8810	W	19960605	

OTHER SOURCE(S): MARPAT 126:99320
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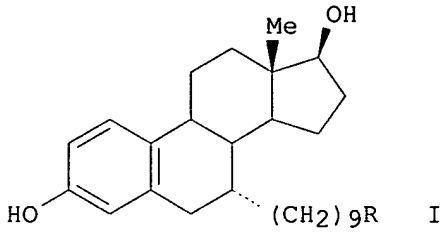

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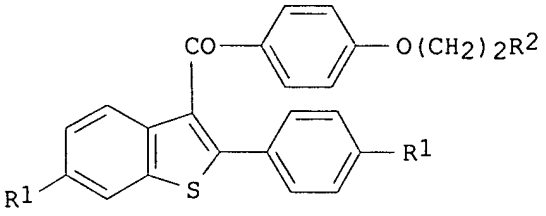


II

AB A method for minimizing the bone loss effect of a compound I [R = -CH2CON(CH3)-CH2CH2CH2CH3 or -SO(CH2)3CF2CF3], or a pharmaceutically acceptable salt thereof, comprising concurrently or sequentially administering to said mammal an effective amount of II [R1 = H, OH, O(C1-4 alkyl), OCOC6H5, OCO(C1-6 alkyl), or OSO2(C4-6 alkyl); R2 = 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino]; or pharmaceutically acceptable salts thereof. Also provided is a method for minimizing bone loss induced by the administration of I comprising concurrently or sequentially administering a bone anabolic agent. A capsule contained raloxifene.HCl 50, starch 150, starch flowable powder 397, silicone fluid 350 cSt 3.0 mg.

L45 ANSWER 4 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:65896 HCAPLUS
DOCUMENT NUMBER: 126:99274
TITLE: **Raloxifene** prevents **bone loss** in lumbar spine and femur in aged ovariectomized rats
AUTHOR(S): Wang, Q.; Hassager, C.; Wang, S.; Riis, B. Juel; Christiansen, C.
CORPORATE SOURCE: Center Clinical and Basic Research, Ballerup, Den.
SOURCE: European Journal of Experimental Musculoskeletal Research (**1995**), 4(3-4), 171-175
CODEN: EJEREE; ISSN: 0803-5288
PUBLISHER: Scandinavian University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Raloxifene has recently been shown to prevent osteopenia in oophorectomized (OVX) young rats. We have investigated the effect of raloxifene on bone mineral content (BMC) and d. (BMD) in more mature rats. One-year-old female Sprague-Dawley rats were divided into five groups: SHAM: Sham operated, placebo treated; OVX: OVX, placebo treated; L-Ral: OVX, 0.1 mg/kg/day per os of raloxifene; H-Ral: OVX, 1.0 mg/kg/day per os of raloxifene and; E2: OVX, 0.5 mg/kg/dag per os of 17-β-estradiol. The rats were killed after 12 wk. The BMC and BMD of the excised left femur and lumbar spine were measured by dual energy X-ray absorptiometry (DXA, Hol. QDR-2000) in vitro. The body weight remained unchanged in the E2

and H-Ral groups, decreased slightly (4%) in the L-Ral group and increased slightly (4-5%) in the SHAM and OVX groups. The increase in body weight in the SHAM and OVX groups was caused by an increase in lean tissue mass (measured by DXA). After 12 wk the OVX group had 6-8% lower BMD at the femur and lumbar spine. The OVX induced osteopenia was prevented by E2 and both doses of raloxifene in the lumbar spine, but only significantly by E2 and low dose raloxifene in the femur. The differences in BMD between the groups were caused by differences in BMC and not by differences in area. We conclude that 0.1 mg/kg/day of raloxifene given orally prevents OVX induced osteopenia in the aged (1-yr-old) rat.

L45 ANSWER 5 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:704467 HCAPLUS
DOCUMENT NUMBER: 126:97
TITLE: Tamoxifen in postmenopausal women. A safety perspective
AUTHOR(S): Robinson, Emily; Kimmick, Gretchen G.; Muss, Hyman B.
CORPORATE SOURCE: Comprehensive Cancer Center, Wake Forest University, Winston-Salem, NC, USA
SOURCE: Drugs & Aging (**1996**), 8(5), 329-337
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 46 refs. Tamoxifen is a synthetic antiestrogen with both agonist and antagonist properties. It is believed to act primarily through binding to estrogen receptors in breast cancer cells, acting as a competitive inhibitor of estrogen. Tamoxifen has a wide range of systemic effects, possibly acting on every estrogen target tissue in the body. Tamoxifen therapy is associated with a significant reduction in the risk of recurrence and death in postmenopausal women with early stage breast cancer. In addition, it has been shown to effectively suppress preclin. breast cancer, as evidenced by the decrease in second primary breast cancers in adjuvant trials. Tamoxifen is also the most widely used endocrine therapy for women with metastatic breast cancer. Tamoxifen, acting predominantly as an estrogen agonist in the liver, has generally favorable effects on serum lipids in postmenopausal women. In addition, tamoxifen has been shown to preserve bone mineral d. and may even decrease the risk of osteoporosis in these women.

L45 ANSWER 6 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:633596 HCAPLUS
DOCUMENT NUMBER: 125:317765
TITLE: Advantages of raloxifene over alendronate or estrogen on nonreproductive and reproductive tissues in the long-term dosing of ovariectomized rats
AUTHOR(S): Sato, Masahiko; Bryant, Henry U.; Iversen, Philip; Helterbrand, Jeff; Smietana, Frank; Bemis, Kerry; Higgs, Richard; Turner, Charles H.; Owan, Ichiro; et al.
CORPORATE SOURCE: Department Endocrine Research, Lilly Research Laboratories, Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1996**), 279(1), 298-305
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB For the first time, raloxifene or alendronate was administered to rats immediately after ovariectomy for 10 mo and compared with estrogen to

elucidate mechanisms behind the raloxifene effects observed in nonreproductive and reproductive tissues. Specifically, 75-day-old rats were randomly selected as sham controls (Sham), ovariectomized controls (Ovx) or ovariectomized rats treated with fully efficacious doses of raloxifene (RA), 17 α-ethynyl estradiol (EE2) or alendronate (ABP). Lumbar vertebrae and proximal tibiae were examined by computed tomog. (QCT) and by histomorphometry. Histomorphometry showed differences in bone architecture between groups when QCT densities were similar, but tibial trabecular bone anal. by QCT correlated with histomorphometry with r = .86 to .93, depending on the parameter. Both techniques confirmed that Ovx had substantially less bone than Sham, with greater loss of trabecular bone in the proximal tibia than vertebrae. Both techniques showed that RA had effects similar to but not identical with EE2 in preventing bone loss in vertebrae and tibiae. ABP partially prevented loss of bone in L-5, but was not significantly different from Ovx in the proximal tibia. This may be caused by ABP suppression of bone apposition, beyond effects observed for EE2 or RA. RA appeared to be more similar to EE2 because ABP significantly depressed bone formation (bone formation rate, mineral apposition rate) to below RA or EE2 levels, especially in L-5. Mech. loading to failure of L-6 vertebrae showed a rank order of vertebral strength of Sham > RA > EE2 > Ovx > ABP, although significant differences were not observed between treatment groups. These data show that ABP suppression of bone formation can affect bone quality with long-term treatment. In other tissues, RA had minimal uterine effects, while significantly lowering serum cholesterol to below EE2-treated levels. Both EE2 and RA rats had significantly lower body wts. than the other groups. ABP had no effect on serum lipids, uterine weight or body weight Therefore, RA appears to have a broader range of desirable effects on bone, body weight, uteri and cholesterol than ABP or EE2 in ovariectomized rats.

L45 ANSWER 7 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:569623 HCAPLUS
DOCUMENT NUMBER: 125:204536
TITLE: Benzothiophene compounds for treating smoking-related bone loss
INVENTOR(S): Leeds, James Patrick
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 724881	A1	19960807	EP 1996-300534	19960125 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5571808	A	19961105	US 1995-381036	19950131
CA 2168067	AA	19960801	CA 1996-2168067	19960125 <--
JP 08231397	A2	19960910	JP 1996-15271	19960131 <--
PRIORITY APPLN. INFO.:			US 1995-381036 A	19950131 <--
OTHER SOURCE(S):	MARPAT 125:204536			

AB A method for treating smoking-related bone loss comprises administering to a human in need thereof a pharmaceutically effective amount of 2-aryl-3-aroylbenzo[b]thiophenes, such as raloxifene. Formulations for capsules and tablets are provided. Oral administration of raloxifene to a rat model of post-menopausal osteoporosis inhibited decrease in femur bone d. in a dose dependent manner.

L45 ANSWER 8 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:546618 HCAPLUS
DOCUMENT NUMBER: 125:266044
TITLE: Benzoquinolin-3-one compounds and methods for inhibiting bone loss
INVENTOR(S): Audia, James E.; Neubauer, Blake L.
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: U.S., 77 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5550134	A	19960827	US 1995-438420	19950510
US 5670514	A	19970923	US 1996-625567	19960328 <--
EP 742010	A2	19961113	EP 1996-303229	19960509 <--
EP 742010	A3	20001011		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CA 2220034	AA	19961114	CA 1996-2220034	19960509 <--
WO 9635422	A1	19961114	WO 1996-US6580	19960509 <--
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9658557	A1	19961129	AU 1996-58557	19960509 <--
ZA 9603694	A	19971110	ZA 1996-3694	19960509 <--
JP 11511739	T2	19991012	JP 1996-534249	19960509 <--
IL 118196	A1	20000629	IL 1996-118196	19960509 <--
PRIORITY APPLN. INFO.:			US 1995-438420	A3 19950510 <--
			WO 1996-US6580	W 19960509

OTHER SOURCE(S): MARPAT 125:266044
AB The present invention provides methods of inhibiting bone loss in women via the administration of an effective amount of a compound from a series of benzoquinolin-3-ones. Such compds. also are sequentially or concurrently coadministered with a **bone antiresorptive** agent (estrogen, **raloxifene**, or alendronate) or a bone anabolic agent (human parathyroid hormone fragments). Preparation of various benzoquinolin-3-ones was presented. E.g., (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one 47 g was methylated with 18.7 g MeI to obtain (4aR)-(10bR)-8-chloro-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one. Capsules were formulated containing (-)-(4aR)-(10bR)-8-chloro-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one 80, premarin 1, Avicel PH 101 50, starch 1500 117.5, silicone oil 2, Tween 80 0.50 and Cab-O-Sil 0.25 mg/capsule, resp.

L45 ANSWER 9 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:483293 HCAPLUS
DOCUMENT NUMBER: 125:158592
TITLE: Zinc-calcium interaction in heparin-induced osteoporotic rabbit plasma
AUTHOR(S): Turan, B.; Delibasi, E.; Sinav, B.; Akkas, N.
CORPORATE SOURCE: Fac. Med., Ankara Univ., Ankara, 06100, Turk.
SOURCE: Trace Elements and Electrolytes (**1996**),

13(3), 138-142
CODEN: TEELEO; ISSN: 0946-2104
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heparin (Liquemin) i.p. (1000 IU/kg/day) was administered to rabbits for 8 wk (group A). Animals of group B were injected calcitonin (100 IU/kg/day) in addition to heparin (1000 IU/kg/day). Animals in group C were medicated like group B and 2 mg/kg/day tamoxifen (Nolvadex) was orally added to their diet. Heparin (A) and heparin + calcitonin (B) treatment caused an increase and a decrease in the blood plasma Ca and Zn levels, resp., whereas addnl. tamoxifen (C) treatment did not alter the Ca level, but the Zn level was still lower than the control. Plasma mineral contents (Na, K, Cl) except P decreased. The estrogen and globulin levels in blood serum increased, whereas the serum albumin and alkaline phosphatase levels decreased. Some alterations in plasma biochem. parameters of heparin-induced osteoporotic animals were observed and some of these alterations were reversed by tamoxifen treatment.

L45 ANSWER 10 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:472404 HCAPLUS
DOCUMENT NUMBER: 125:185773
TITLE: Time-dependent changes in biochemical bone markers and serum cholesterol in ovariectomized rats: Effects of raloxifene HCl, tamoxifen, estrogen, and alendronate
AUTHOR(S): Frolik, C. A.; Bryant, H. U.; Black, E. C.; Magee, D. E.; Chandrasekhar, S.
CORPORATE SOURCE: Endocrine Research, Lilly Research Laboratories, Indianapolis, IN, 46285, USA
SOURCE: Bone (New York) (**1996**), 18(6), 621-627
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bone loss associated with postmenopausal osteoporosis can be reduced by treatment with anti-resorptive agents such as estrogen or bisphosphonates. Whereas bisphosphonates primarily affect bone loss, estrogens have an advantage of also lowering serum cholesterol levels, although they have a detrimental effect in the uterus. Recently, raloxifene HCl, a selective estrogen receptor modulator (SERM), has been shown to decrease both bone loss and cholesterol levels without the neg. uterine effects. These anti-resorptive agents reduce bone turnover, which can be evaluated by measuring bone turnover markers. To compare the effects of estrogen, 2 SERMs (raloxifene HCl and tamoxifen), and alendronate, a bisphosphonate that inhibits bone loss by an estrogen-independent pathway, on metabolic bone markers and cholesterol levels, rats were ovariectomized 2 wk prior to 3 wk of daily oral treatment with raloxifene HCl (3 mg/kg), ethynyl estradiol (0.1 mg/kg), tamoxifen (3 mg/kg), or alendronate (3 mg/kg). Raloxifene HCl, tamoxifen, and ethynyl estradiol reduced serum cholesterol to levels below control values within 4 days after initiation of treatment, whereas alendronate had no effect. After 3 wk of treatment, serum cholesterol values in ethynyl estradiol treated animals, although still below the control value, had risen 6.4-fold; raloxifene HCl and tamoxifen values rose by only 1.4-1.5-fold. Therefore, compared with estrogen, SERMs may have a longer-term suppressive effect on serum cholesterol. At 4 days of treatment, ovariectomized rats had a 1.4-fold increase in serum osteocalcin level compared with controls. Ethynyl estradiol lowered this level within 1 wk of treatment by 18%, with a more pronounced reduction of 34% at 3 wk. In contrast, raloxifene HCl, tamoxifen, or alendronate had very little effect after the 1st week (6 to 13% reduction),

although there was an 18 to 25% reduction by 3 wk. Urinary pyridinoline levels, elevated 1.4-fold in the ovariectomized rat compared with controls 2 wk after surgery, were reduced to control values after 2 wk of treatment with raloxifene HCl, ethynyl estradiol, tamoxifen, or alendronate. These data support the concept that estrogen, raloxifene HCl, **tamoxifen**, and alendronate inhibit **bone loss** in the ovariectomized animal by reducing bone resorption. The results also indicate that for treatment of postmenopausal **osteoporosis**, **raloxifene** HCl may have an advantage over the other anti-resorptives studied in having both non-uterotrophic and hypocholesterolemic effects in addition to its ability to inhibit bone resorption.

L45 ANSWER 11 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:370832 HCAPLUS
DOCUMENT NUMBER: 125:49586
TITLE: Raloxifene, tamoxifen, nafoxidine, or estrogen effects on reproductive and nonreproductive tissues in ovariectomized rats
AUTHOR(S): Sato, Masahiko; Rippy, Marian K.; Bryant, Henry U.
CORPORATE SOURCE: Dep. of Endocrine Research, Lilly Research Lab., Indianapolis, IN, 46285, USA
SOURCE: FASEB Journal (**1996**), 10(8), 905-912
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB For the first time, four well-characterized compds. from four distinct chemical classes were directly compared for efficacy and potency in bone, uteri, lipids, and adipose tissues in an ovariectomized model with 6 mo old rats. Five weeks of oral dosing confirmed that ethynylestradiol, tamoxifen, and raloxifene are potent inhibitors of the loss in volumetric bone mineral d. (BMD, mg/mL) induced by ovariectomy, as measured by computed tomog. In the metaphysics of distal femora from ovariectomized rats, anal. showed a significant 12-20% decrease in the BMD. Linear regression anal. was used to calculate half-maximal efficacious doses for ethynylestradiol ED50 = 0.04 mg/kg, which was threefold more potent than raloxifene, which in turn was threefold more efficacious than nafoxidine. In the uterus, raloxifene had minimal effects on the endometrium and smaller effects on uterine eosinophil peroxidase activity than nafoxidine, tamoxifen, or estrogen, resp. Estrogen was the most potent in reducing cholesterol levels in ovariectomized rats, whereas tamoxifen and nafoxidine were more effective than raloxifene in blocking gain in body weight Distinct compds. had advantages in the management of bone, uterine, serum cholesterol, and adipose tissues after ovariectomy. The distinct pattern of pharmacol. effects may be best understood in terms of their resp. chemical structure, specifically estrogens, benzothiophenes (raloxifene), dihydronaphthylenes (nafoxidine), and triphenylethylenes (tamoxifen). These data point to advantages of sep. compds. in the management of bone, uterine, serum cholesterol, and adipose tissues after estrogen deficiency, and show that the benzothiophene raloxifene has potentially important advantages over estrogen, tamoxifen, or nafoxidine in the uterus.

L45 ANSWER 12 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:312445 HCAPLUS
DOCUMENT NUMBER: 125:25752
TITLE: Regulation of avian osteoclastic H+-ATPase and **bone resorption** by **tamoxifen**

and calmodulin antagonists. Effects independent of steroid receptors
AUTHOR(S): Williams, John P.; Blair, Harry C.; McKenna, Margaret A.; Jordan, S. Elizabeth; McDonald, Jay M.
CORPORATE SOURCE: Dep. Pathol., Univ. Alabama, Birmingham, AL, 35294, USA
SOURCE: Journal of Biological Chemistry (**1996**), 271(21), 12488-12495
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We used highly purified chicken osteoclasts and isolated membranes from osteoclasts to study effects of tamoxifen, 4-hydroxytamoxifen, calmodulin antagonists, estrogen, diethylstilbestrol, and the anti-estrogen ICI 182780 on cellular degradation of 3H-labeled bone in vitro and on membrane HCl transport. Bone resorption was reversibly inhibited by tamoxifen, 4-hydroxytamoxifen, and trifluoperazine with IC50 values of .apprx.1 μM. Diethylstilbestrol and 17-β-estradiol had no effects on bone resorption at receptor-saturating concns., while ICI 182780 inhibited bone resorption at concns. greater than 1 μM. At these concns. ICI 182780, like tamoxifen, inhibits calmodulin-stimulated cyclic nucleotide phosphodiesterase activity. Membrane HCl transport, assessed by ATP-dependent acridine orange uptake, was unaffected by 17-β-estradiol and diethylstilbestrol at concns. up to 10 μM, whole ICI 182780 inhibited HCl transport at concns. greater than 1 μM. In contrast HCl transport was inhibited by tamoxifen, 4-hydroxytamoxifen, and the calmodulin antagonists, trifluoperazine and calmidazolium, with IC50 values of 0.25-1.5 μM. These results suggested the presence of a membrane-associated non-steroid receptor for tamoxifen in osteoclasts. Tamoxifen binding studies demonstrated saturable binding in the osteoclast particulate fraction, but not in the nuclear or cytosolic fractions. Membranes enriched in ruffled border by differential centrifugation following nitrogen cavitation showed binding consistent with one site, Kd .apprx.1 μM. Our findings indicate that tamoxifen inhibits osteoclastic HCl transport by binding membrane-associated target(s), probably similar or related to calmodulin antagonist targets. Further, effects of estrogens or highly specific anti-estrogens on bone turnover do not support the hypothesis of a direct effect on osteoclasts by these compds. in this species.

L45 ANSWER 13 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:194267 HCAPLUS
DOCUMENT NUMBER: 124:279093
TITLE: The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women
AUTHOR(S): Grey, Andrew B.; Stapleton, Joanne P.; Evans, Margaret C.; Tatnell, Michele A.; Ames, Ruth W.; Reid, Ian R.
CORPORATE SOURCE: Department Medicine, University Auckland, Auckland, N. Z.
SOURCE: American Journal of Medicine (**1995**), 99(6), 636-41
CODEN: AJMEAZ; ISSN: 0002-9343
PUBLISHER: Excerpta Medica
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of antiestrogenic agent tamoxifen on bone mineral d. in normal late postmenopausal women was examined A randomized, double-blind, placebo-controlled trial was performed with 57 healthy, late

postmenopausal women (mean 11 yr since menopause). Subjects were assigned to take either tamoxifen 20 mg/d or placebo for 2 yr. Total body, lumbar spine, and proximal femoral (femoral neck, Ward's triangle, trochanter) bone mineral densities were measured every 6 mo using dual-energy x-ray absorptiometry. Serum and urine indexes of bone turnover were measured at baseline, 6 mo, and 2 yr. In the women given tamoxifen, the mean bone mineral d. of the lumbar spine increased by 1.4%, while that in the women given placebo declined by 0.7% (for difference between groups). Total body bone mineral d. declined in both groups, but less so in the tamoxifen-treated women. At both sites, the effect of tamoxifen was maximal after 1 yr, with no further separation of the groups thereafter. There was no significant effect of tamoxifen on bone mineral d. in the proximal femur. Tamoxifen produced significant falls in serum alkaline phosphatase, ionized calcium, and phosphate, and in urinary excretion of hydroxyproline, n-telopeptides, and calcium (for each). In normal late postmenopausal women, tamoxifen at a dose of 20 mg/d exerts a small protective effect on bone mineral d., comparable in magnitude to that of calcium supplementation and less than that of either estrogen or the bisphosphonates. Tamoxifen is unlikely to supersede any of these therapies in the management of postmenopausal osteoporosis.

L45 ANSWER 14 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:175678 HCAPLUS
DOCUMENT NUMBER: 124:212066
TITLE: Pharmaceutical compositions containing a bisphosphonate and an anti-resorptive agent for inhibiting bone loss
INVENTOR(S): Black, Larry John; Cullinan, George Joseph
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 693285	A2	19960124	EP 1995-305083	19950720 <--
EP 693285	A3	19980506		
EP 693285	B1	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
ZA 9506029	A	19970120	ZA 1995-6029	19950719 <--
NZ 272608	A	20000526	NZ 1995-272608	19950719 <--
TW 398975	B	20000721	TW 1995-84107488	19950719 <--
PL 181304	B1	20010731	PL 1995-309693	19950719 <--
NO 9502890	A	19960123	NO 1995-2890	19950720 <--
NO 308194	B1	20000814		
AU 9527112	A1	19960201	AU 1995-27112	19950720 <--
AU 693235	B2	19980625		
HU 72754	A2	19960528	HU 1995-2193	19950720 <--
RU 2149631	C1	20000527	RU 1995-114385	19950720 <--
IL 114683	A1	20010614	IL 1995-114683	19950720 <--
AT 212846	E	20020215	AT 1995-305083	19950720 <--
ES 2168336	T3	20020616	ES 1995-305083	19950720 <--
PT 693285	T	20020628	PT 1995-305083	19950720 <--
CA 2154414	AA	19960123	CA 1995-2154414	19950721 <--
JP 08040911	A2	19960213	JP 1995-185512	19950721 <--
BR 9503406	A	19960227	BR 1995-3406	19950721 <--
CN 1119940	A	19960410	CN 1995-108916	19950721 <--

CN 1079671 B 20020227
US 2001051636 A1 20011213 US 2000-520737 20000308 <--
PRIORITY APPLN. INFO.: US 1994-279363 A 19940722 <--
OTHER SOURCE(S): MARPAT 124:212066
AB A method for inhibiting bone loss comprises administering to a human in need thereof a first compound selected from (1) triarylethylenes; (2) 2,3-diaryl-2H-1-benzopyrans, (3) 1-aminoalkyl-2-phenylindoles; (4) 2-phenyl-3-aroylbenzothiophenes, (5) 1-substituted-2-aryl-dihydronaphthalenes; of (6) benzofurans, and a second compound being a bisphosphonate or pharmaceutically acceptable salts and solvates thereof. Combination of 0.1 mg/kg raloxifene and 0.1 mg/kg alendronate demonstrated the greatest protection from bone loss in post-menopausal osteoporosis model in rats with the lowest exposure to the potentially undesirable side-effects of alendronate. Pharmaceutical formulations containing above combination are disclosed.

L45 ANSWER 15 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:163183 HCAPLUS
DOCUMENT NUMBER: 124:250081
TITLE: Elemental composition of bone minerals in women with breast cancer treated with adjuvant tamoxifen
AUTHOR(S): Kalef-Ezra, J. A.; Pavlidis, N.; Klouvas, G.; Karantanas, A.; Hatzikonstantinou, I.; Glaros, D.
CORPORATE SOURCE: Medical School, University Ioannina, Ioannina, 451 10, Greece
SOURCE: Breast Cancer Research and Treatment (**1996**), 38(2), 161-8
CODEN: BCTRD6; ISSN: 0167-6806
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Estrogen levels play a major role in conditioning the rates of bone changes in women. Tamoxifen is a synthetic estrogen antagonist commonly used as an adjuvant therapy for breast cancer. The goal of the present study was to study the amount and the elemental composition of bone minerals in the appendicular skeleton of women with breast cancer treated with adjuvant tamoxifen, as well as to investigate the possibility of increased risk for osteoporosis. Forty-two patients, aged 41-65 yr, without skeletal metastases were studied. The mean duration of tamoxifen administration on a daily dose of 20 mg was 21 mo (range 1-59 mo). It was found that neither the amount of phosphorus in hands (HBP) nor forearm bone mineral content (BMC) differ statistically from those of age-matched healthy subjects. This was confirmed by reassessing bone mineral status after 30 mo in 17 postmenopausal patients treated with tamoxifen for a mean time of 52 mo. In conclusion, our data support that long-term tamoxifen treatment has no adverse or protective effect on the amount and elemental composition of the appendicular skeleton.

L45 ANSWER 16 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:82434 HCAPLUS
DOCUMENT NUMBER: 124:134461
TITLE: Organ-selective actions of tamoxifen and other partial antiestrogens
AUTHOR(S): Turner, R. T.
CORPORATE SOURCE: Dep. Orthop. Res., Mayo Clin. Found., Rochester, NY, 55905, USA
SOURCE: Ernst Schering Research Foundation Workshop (**1995**), 16, 65-84
CODEN: ESRWEL; ISSN: 0947-6075
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English
AB A review with many refs. of prevention of and therapy for postmenopausal osteoporosis with estrogen agonists and antagonists.

L45 ANSWER 17 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:17239 HCAPLUS
DOCUMENT NUMBER: 124:106966
TITLE: Effects of droloxifene on prevention of cancellous bone loss and bone turnover in the axial skeleton of aged, ovariectomized rats
AUTHOR(S): Ke, H. Z.; Chen, H. K.; Qi, H.; Pirie, C. M.; Simmons, H. A.; Ma, Y. F.; Jee, W. S. S.; Thompson, D. D.
CORPORATE SOURCE: Department Metabolic Diseases, Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Bone (New York) (**1995**), 17(5), 491-6
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to determine the efficacy of droloxifene (DRO), an estrogen antagonist/agonist, in preventing ovariectomy (OVX)-induced lumbar vertebral cancellous bone loss and bone turnover in aged female rats. Fifty-three Sprague-Dawley female rats were OVX or sham-operated at 19 mo of age, and divided into 6 groups: (I) sham-operated controls; (II) OVX vehicle controls; (III) OVX rats treated with E2 at 30 μg/kg/day; (IV)-(VI) OVX rats treated with DRO at either 2.5, 5, or 10 mg/kg p.o. daily. The treatment period was 8 wk. Static and dynamic cancellous bone histomorphometric parameters were determined on 4 and 10 μm thick, undecalcified, double-fluorescent labeled sections of the fourth lumbar vertebral body. Changes in body weight, uterine weight, and total serum cholesterol were also determined OVX for 8 wk in 19-mo-old female rats resulted in reduced trabecular bone volume (-18%) and trabecular width (-10%) and increased labeling perimeter (+52%), bone formation rate/bone surface referent (+60%), bone formation rate/bone volume referent (+77%), osteoclast number (+41%), and osteoclast perimeter (+41%). E2 treatment at 30 μg/kg/day for 8 wk prevented OVX-induced cancellous bone loss and decreased bone resorption, bone formation, and bone turnover to the values of sham controls. DRO at 2.5-10 mg/kg/day completely prevented bone loss and bone turnover associated with estrogen deficiency. Osteoclast number and perimeter were significantly decreased in DRO-treated-OVX rats compared to both sham and OVX controls. Trabecular bone volume, trabecular width, labeling perimeter, bone formation rate/bone surface referent, and bone formation rate/bone volume referent showed no differences in DRO-treated OVX rats compared to those of E2-treated OVX rats and sham controls. These histomorphometric results indicated that DRO is an estrogen agonist on cancellous bone of lumbar vertebral bodies of aged, OVX rats. Further, E2 treatment prevented the OVX-induced increase in body weight gain and nonsignificantly reduced total serum cholesterol compared to OVX controls. Body weight gain and total serum cholesterol did not differ between OVX rats treated with E2 and sham controls. In OVX rats treated with DRO, body weight decreased significantly in a dose-response manner, and total serum cholesterol was significantly reduced by 65% to 70% compared to both sham and OVX controls. In addition, treatment with E2 increased uterine weight to the value of sham controls in OVX rats. However, DRO had no effect on uterine weight at either 2.5 or 10 mg/kg/day, while it only slightly but significantly increased uterine weight over OVX controls at 5 mg/kg/day. The authors conclude that DRO was efficacious in the prevention of lumbar vertebral cancellous bone loss and in the decline of total serum cholesterol but had no effect on uterine weight in the aged, OVX female rats. The data suggest that DRO is a potentially useful agent for the prevention

of vertebral bone loss leading to spinal fractures in postmenopausal women.

L45 ANSWER 18 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:917587 HCAPLUS
DOCUMENT NUMBER: 123:330279
TITLE: Raloxifene is a tissue-selective agonist/antagonist that functions through the estrogen receptor
AUTHOR(S): Fuchs-Young, R.; Glasebrook, A. L.; Short, L. L.; Draper, M. W.; Rippy, M. K.; Cole, H. W.; Magee, D. E.; Termine, J. D.; Bryant, H. U.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Annals of the New York Academy of Sciences (**1995**), 761(Steroid Receptors and Antihormones), 355-60
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Raloxifene appears to be a selective estrogen receptor modulator that has beneficial estrogen-like properties in saving bone and lowering lipids. Raloxifene has the advantage of inhibiting proliferation in breast epithelium and uterine endometrium. This compound has the potential of being useful as a treatment for osteoporosis as well as helpful in understanding tissue-specific responses of antisteroids.

L45 ANSWER 19 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:804467 HCAPLUS
DOCUMENT NUMBER: 123:188619
TITLE: Combination of 2-phenyl-3-aroylbenzothiophenes with progestins for treatment of osteoporosis
INVENTOR(S): Black, Larry John; Cullinan, George Joseph
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
EP 665015	A2	19950802	EP 1995-300439	19950125	<--
EP 665015	A3	19980408			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
US 5591753	A	19970107	US 1994-189399	19940128	
CA 2140952	AA	19950729	CA 1995-2140952	19950124	<--
AU 9511390	A1	19950810	AU 1995-11390	19950124	<--
AU 692811	B2	19980618			
ZA 9500556	A	19960724	ZA 1995-556	19950124	<--
NZ 286930	A	20000728	NZ 1995-286930	19950124	<--
TW 401296	B	20000811	TW 1995-84100589	19950124	<--
CZ 290045	B6	20020515	CZ 1995-176	19950124	<--
NO 9500275	A	19950731	NO 1995-275	19950125	<--
HU 72633	A2	19960528	HU 1995-229	19950125	<--
JP 07267858	A2	19951017	JP 1995-10490	19950126	<--
CN 1111511	A	19951115	CN 1995-101458	19950126	<--
CN 1084617	B	20020515			
IL 112455	A1	19991231	IL 1995-112455	19950126	<--

RU 2181048	C2	20020410	RU 1995-101044	19950126 <--
US 5646137	A	19970708	US 1996-700184	19960820 <--
PRIORITY APPLN. INFO.:			US 1994-189399	A 19940128 <--
			NZ 1995-270386	A1 19950124 <--

OTHER SOURCE(S): MARPAT 123:188619

AB A new method for treating osteoporosis and inhibition of bone loss comprises administering 2-phenyl-3-aroylbenzothiophene derivs. (Markush structure given) together with a progestin selected from medroxyprogesterone, norethindrone or norethynodrel, or a pharmaceutically acceptable salt thereof. Rats were ovariectomized to induce post-menopausal osteoporosis and were treated daily with combination of 10 mg/kg ethynylestradiol and 10 mg/kg raloxifene for 35 days, then they were sacrificed and femurs excised and scanned. The femur d. was 61.528 as compared to 42.403 for the non-ovariectomized controls.

L45 ANSWER 20 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:730370 HCAPLUS

DOCUMENT NUMBER: 123:160785

TITLE: **Droloxifene** prevents ovariectomy-induced **bone loss** in tibiae and femora of aged female rats: a dual-energy x-ray absorptiometric and histomorphometric study

AUTHOR(S): Chen, Hong Ka; Ke, Hua Zhu; Jee, Webster S. S.; Ma, Yan Fei; Pirie, Christine M.; Simmons, Hollis A.; Thompson, David D.

CORPORATE SOURCE: Division of Radiobiology, Univ. of Utah Sch. of Medicine, Salt Lake City, UT, USA

SOURCE: Journal of Bone and Mineral Research (**1995**), 10(8), 1256-62
CODEN: JBMREJ; ISSN: 0884-0431

PUBLISHER: Liebert

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Our previous studies indicated that droloxifene (DRO), a tissue-specific estrogen antagonist/agonist, prevented bone loss without causing uterine hypertrophy is growing ovariectomized (OVX) rats. Using dual-energy x-ray absorptiometry (DXA) and bone histomorphometry, the current study compared the efficacy of DRO to 17β-estradiol (E2) in preventing OVX-induced bone loss in tibiae and femora of 19-mo-old rats to determine whether DRO had similar skeletal effects as E2 in aged female rats. Sprague-Dawley female rats were OVX or sham-operated (sham) at 19 mo of age. The sham-operated rats were treated with vehicle (oral), while the OVX rats were treated with vehicle (oral), E2 at 30 μg/kg/day (s.c.), or DRO at 2.5, 5, or 10 mg/kg/day (oral) for 8 wk. Bone mineral d. (BMD) of whole femora (WF), distal femoral metaphyses (DFM), femoral shafts (FS), and proximal femora (PF) was determined using DXA. Static and dynamic cancelous bone histomorphometric analyses were performed in double-labeled undecalcified longitudinal sections from proximal tibial metaphyses. Ovariectomy for 8 wk significantly reduced the BMD of WF, DFM, FS, and PF (from -6 to -15%). Treatment with E2 completely prevented the decreases in BMD of WF and DFM and had no significant effects in BMD of FS and PF in aged OVX rats. The decrease in BMD of DFM induced by OVX was prevented by treatment with DRO at all dose levels. In addition, DRO at 10 mg/kg/day prevented OVX-induced decreases in BMD of WF, FS, and PF. Furthermore, proximal tibial cancellous bone histomorphometric results showed that OVX significantly decreased the trabecular bone volume by 34% and increased the activation frequency by 104% while it nonsignificantly increased other indexes including percent eroded perimeter, mineral apposition rate, and bone formation rate per bone volume compared with sham-operated controls. Treatment with E2 or DRO at all dose levels completely prevented the

OVX-induced decreases in trabecular bone volume and increases in bone turnover, indicating that DRO is an estrogen agonist in bone in aged OVX rats. Together with the previous findings that DRO inhibited body weight gain, reduced total serum cholesterol, and had no effect on uterine weight, we conclude that DRO is as efficacious as E2 in preventing OVX-induced bone loss and inhibiting bone turnover but without estrogenic uterine effects in aged OVX rats. These data suggest that DRO may be superior to E2 for the treatment of postmenopausal and senile osteoporosis.

L45 ANSWER 21 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:681411 HCAPLUS
DOCUMENT NUMBER: 123:103343
TITLE: Prostaglandin E2 administration prevents bone loss induced by orchidectomy in rats
AUTHOR(S): Li, M.; Jee, W. S. S.; Ke, H. Z.; Tang, L. Y.; Ma, Y. F.; Liang, X. G.; Setterberg, R. B.
CORPORATE SOURCE: School Medicine, University Utah, Salt Lake, UT, 84112, USA
SOURCE: Journal of Bone and Mineral Research (**1995**), 10(1), 66-73
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objects of this study were to investigate whether prostaglandin E2 (PGE2) can prevent orchidectomy (ORX)-induced cancellous bone loss in growing male rats, and to determine the differential effects of PGE2 on sham-operated (sham) and ORX male rats. Fourteen-week-old Sprague-Dawley male rats were divided into groups of basal, vehicle-treated sham, PGE2-treated sham, vehicle-treated ORX, and PGE2-treated ORX rats for either 3 or 9 wk. PGE2 was given at 6 mg/kg body weight daily by s.c. injection. Static and dynamic cancellous bone histomorphometry were performed on double-fluorescent labeled undecalcified proximal tibial metaphyseal sections. No effect was observed by ORX on body weight or longitudinal bone growth rate when compared with sham-operated controls. However, androgen deficiency caused significant increases in percent eroded perimeter, mineral apposition rate, and bone turnover (bone-volume-referent-bone formation rate), which resulted in a significant decrease in trabecular bone number, increase in trabecular separation, and a nonsignificant decrease in trabecular bone area by 3 wk of ORX. After 9 wk of ORX, trabecular bone area and number were significantly decreased, and trabecular separation, percent eroded perimeter, and the index of bone turnover (bone-volume-referent-bone formation rate) remained significantly increased while the index of bone formation (tissue-volume-referent-bone formation rate) was nonsignificantly decreased when compared with sham controls. When 6 mg PGE2/kg/day was given for 3 and 9 wk, similar anabolic effects were observed in sham and ORX rats. PGE2 caused significant decreases in body weight and longitudinal bone growth rate and significant increases in trabecular bone area, thickness, labeling perimeter, mineral apposition rate, and tissue-volume-referent-bone formation rate in both sham and ORX rats when compared with their resp. controls. In sham-operated rats, PGE2 had no effect on percent eroded perimeter after 3 wk of treatment, whereas after 9 wk PGE2 caused a significant increase in this index. PGE2 partially inhibited the increase in percent eroded perimeter induced by ORX at week 3, but had no effect on this parameter at week 9 as compared with ORX controls. In summary, the new findings from current study indicated that **PGE2** can prevent **bone loss** induced by ORX and the anabolic skeletal effect of PGE2 independent of the presence of androgen and longitudinal growth and occurs mainly on the pre-existing bone surface.

L45 ANSWER 22 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:575349 HCAPLUS
DOCUMENT NUMBER: 122:306275
TITLE: Droloxifene, a new estrogen antagonist/agonist, prevents bone loss in ovariectomized rats
AUTHOR(S): Ke, Hua Zhu; Simmons, Hollis A.; Pirie, Christine M.; Crawford, D. Todd; Thompson, David D.
CORPORATE SOURCE: Dep. Cardiovascular Metabolic Siseases, Central Res. Div., Groton, CT, 06340, USA
SOURCE: Endocrinology (**1995**), 136(6), 2435-41
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to determine the effects of droloxifene (DRO), a new estrogen antagonist/agonist, on bone turnover, bone mass, total serum cholesterol, and uterine weight in rats made estrogen deficient by ovariectomy. Sprague-Dawley female rats were ovariectomized (OVX) or sham operated (sham) at 5 mo of age and treated with 17β-estradiol (E2) at 30 μg/kg, s.c., daily or with DRO at 5, 10, or 20 mg/kg·day, orally, for 4 wk. At the time of death, body weight gain, uterine weight, and total serum cholesterol were measured. Bone area, bone mineral content (BMC), and bone mineral d. (BMD) of whole femora, distal femoral metaphases, femoral shaft, and proximal femora were determined ex vivo using dual energy x-ray absorptiometry. Static and dynamic cancellous bone histomorphometric anal. of proximal tibial metaphyses was performed in double fluorescent labeled, undecalcified, 4- and 10-μm longitudinal sections. Body weight gain in E2-treated OVX rats was significantly reduced compared to that in OVX controls, but was not different from that in sham controls. Body weight gain in DRO-treated OVX rats was decreased significantly compared to that in both sham and OVX controls. In OVX rats, uterine weight was completely preserved by treatment with E2. Uterine weight in DRO-treated OVX rats was slightly, but significantly, increased from the vehicle-treated control value, and was significantly lower than that in sham controls and E2-treated OVX rats. Treatment with s.c. injection of E2 in OVX rats had no effect on total serum cholesterol, whereas OVX rats orally treated with DRO at 5-20 mg/kg·day decreased total serum cholesterol by 33-46% compared to levels in sham and OVX controls. Compared to sham controls, OVX decreased BMC and BMD of distal femoral metaphyses, increased BMD of the femoral shaft, and had no effect on BMC and BMD of whole femora and proximal femora. Treatment with either E2 or DRO prevented these changes induced by OVX. Proximal tibial metaphyseal trabecular bone volume and trabecular number were increased, and trabecular separation, percent osteoclast perimeter, osteoclast number, percent mineralizing perimeter, mineral apposition rate, bone formation rate, and bone turnover rate were decreased in 5, 10, or 20 mg/kg·day DRO-treated OVX rats compared to OVX controls. These cancellous bone histomorphometric indexes in DRO-treated OVX rats did not differ from those in E2-treated OVX rats or sham controls, suggesting that DRO completely prevented the increases in bone turnover and the decrease in bone mass induced by OVX in rats. The results demonstrate that DRO prevented increased bone turnover and bone loss, reduced total serum cholesterol, and caused minimal uterine hypertrophy in 5-mo-old OVX rats. These data suggest that DRO is an estrogen agonist on bone and may be an effective alternative to estrogen for the prevention of postmenopausal osteoporosis.

L45 ANSWER 23 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:562397 HCAPLUS

DOCUMENT NUMBER: 123:690
TITLE: Tamoxifen directly stimulates the mineralization of human osteoblast-like osteosarcoma cells through a pathway independent of estrogen response element
AUTHOR(S): Takeuchi, Masakazu; Tokin, Masahiro; Nagata, Kiyoshi
CORPORATE SOURCE: Shionogi Res. Lab., Shionogi and Co., Ltd., Osaka, 553, Japan
SOURCE: Biochemical and Biophysical Research Communications (**1995**), 210(2), 295-301
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tamoxifen, an estrogen antagonist, stimulated the mineralization of osteoblasts in vitro in a dose-dependent manner in the presence of inorg. phosphate. The mechanism of mineralization by tamoxifen was different from that by 1α,25-dihydroxyvitamin D3. In addition, tamoxifen did not activate estrogen-response-element-mediated transcription in osteoblasts. These findings suggest that tamoxifen directly stimulates the mineralization of osteoblasts through a pathway independent of the conventional estrogen-response-element-mediated gene expression.

L45 ANSWER 24 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:489933 HCAPLUS
DOCUMENT NUMBER: 122:232636
TITLE: Raloxifene-responsive element-reporter gene constructs and identification of anti-osteoporosis agents with recombinant cells containing these constructs
INVENTOR(S): Yang, Na Nora
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 65 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 629697	A2	19941221	EP 1994-304432	19940620 <--
EP 629697	A3	19950419		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5445941	A	19950829	US 1993-81610	19930621 <--
ZA 9404160	A	19951213	ZA 1994-4160	19940613 <--
IL 109990	A1	19990620	IL 1994-109990	19940613 <--
AU 9464701	A1	19941222	AU 1994-64701	19940614 <--
AU 677319	B2	19970417		
NO 9402313	A	19941222	NO 1994-2313	19940617 <--
CA 2126294	AA	19941222	CA 1994-2126294	19940620 <--
FI 9402958	A	19941222	FI 1994-2958	19940620 <--
BR 9402480	A	19950125	BR 1994-2480	19940620 <--
CN 1102437	A	19950510	CN 1994-106717	19940620 <--
JP 07184661	A2	19950725	JP 1994-137287	19940620 <--
HU 70326	A2	19950928	HU 1994-1851	19940620 <--
PL 177706	B1	20000131	PL 1994-303915	19940620 <--
AU 9728710	A1	19970925	AU 1997-28710	19970717 <--
PRIORITY APPLN. INFO.:			US 1993-81610 A	19930621 <--
			US 1994-246990 A	19940518 <--

AB The present invention relates to methods for the identification of therapeutic agents for the treatment of osteoporosis. The invention

relates to isolating, cloning, and using nucleic acids from the promoter regions of transforming growth factor β genes comprising novel regulatory elements designated "raloxifene responsive elements" (RRE). The invention also encompasses eukaryotic cells containing such RRE operably linked to reporter genes such that the RRE modulate the transcription of the reporter genes. The invention provides methods for identifying anti-osteoporosis agents that induce transcription of genes operably linked to such RRE without inducing deleterious or undesirable side effects associated with current anti-osteoporosis therapy regimens. An RRE was identified in the promoter regions of the genes for TGF-β1, TGF-β2, and TGF-β3. In contrast to ERE, the RRE responded more strongly to the antiestrogen raloxifene than to estrogen. The estrogen receptor was necessary for the activity of raloxifene. Different domains of the receptor were responsible for estrogen and raloxifene effects on gene expression. Reporter plasmids containing the TGF-β3 RRE fused to the CAT or luciferase gene and MCF-7 cells stably transformed with such plasmids were prepared and used in a method for screening for potential anti-osteoporosis agents.

L45 ANSWER 25 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:445248 HCAPLUS
DOCUMENT NUMBER: 122:205484
TITLE: Effects of estradiol and tamoxifen on oxytocin-induced phospholipase C activation in human myometrial cells
AUTHOR(S): Phaneuf, S.; Europe-Finner, G. N.; MacKenzie, I. Z.; Watson, S. P.; Bernal, A. Lopez
CORPORATE SOURCE: John Radliffe Hospital, University of Oxford, Oxford, OX3 9DU, UK
SOURCE: Journal of Reproduction and Fertility (**1995**), 103(1), 121-6
CODEN: JRPFA4; ISSN: 0022-4251
PUBLISHER: Journals of Reproduction and Fertility Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of estradiol in the control of uterine responsiveness to oxytocin was investigated by measuring oxytocin-induced phospholipase C activation in [3H]inositol-labeled cultured human myometrial cells. Addition of estradiol to steroid-free culture medium (10% (volume/volume) fetal calf serum treated with dextran-coated charcoal in phenol red-free medium) enhanced formation of inositol phosphates and this effect was completely abolished by the anti-estrogen tamoxifen. The inhibitory of tamoxifen on oxytocin-induced phospholipase C activation occurred in both steroid-free and complete culture medium; it was time- and concentration-dependent and was only partly reversed by estradiol. When phospholipase C was activated with **PGF2a** or fluoroaluminate instead of oxytocin, estradiol and **tamoxifen** had the same stimulatory and inhibitory effects, resp. The inhibitory effect of tamoxifen could not be prevented by treating the cells with pertussis toxin. Moreover, the effect of tamoxifen was not mediated by inhibition of protein kinase C, since the use of staurosporine (a protein kinase inhibitor) resulted in potentiation of phospholipase C activation by oxytocin. Both estradiol and tamoxifen increased [3H]inositol incorporation into cellular lipids and cell proliferation. These results suggest that estradiol enhances myometrial responsiveness to oxytocin and other agonists by facilitating phospholipase C activation at a post-receptor level. This effect is antagonized by tamoxifen; however, tamoxifen also has estrogen-independent inhibitory effects.

L45 ANSWER 26 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:439736 HCAPLUS
DOCUMENT NUMBER: 122:205142

TITLE: Longitudinal and cross-sectional analysis of raloxifene effects on tibiae from ovariectomized aged rats
AUTHOR(S): Sato, Masahiko; Kim, John; Short, Lorri L.; Slemenda, Charles W.; Bryant, Henry U.
CORPORATE SOURCE: Dep. Endocrine Res., Indiana Univ. Sch. Med., Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1995**), 272(3), 1252-9
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To extend and confirm previous data, we examined the effects of raloxifene on the proximal tibia of ovariectomized rats, aged 6 mo, longitudinally and cross-sectionally, by computed tomog. (pQCT) and then compared the effects to those of orally dosed estrogen. Comparative anal. of phantoms and rat bones showed that the pQCT is precise and correlates with a Hol. QDR 1000W (DXA) with R = 0.999 but is capable of measuring significant differences between groups when the DXA cannot. This may reflect the ability of the pQCT to determine bone volume, mineral content (mg) and volumetric mineral d. (mg/cm3), compared with two-dimensional analyses performed with DXA. Longitudinal anal. of the proximal tibia in vivo showed a significant 17% reduction in mineral d. 31 days after ovariectomy. Examination of the images from ovariectomized rats showed a progressive increase in the cross-sectional area of the proximal tibiae, loss of trabecular bone, widening of marrow spaces and thinning of the cortical bone wall opposite the fibula. Regression anal. of the dose-dependent protective effects of raloxifene showed the half-maximal efficacy on tibiae mineral d. to be ED50 = 0.4 mg/kg/day per os by pQCT and 0.2 mg/kg/day by DXA. By comparison, 17α ethynyl estradiol showed dose-dependent effects with ED50 = 0.013 mg/kg/day per os by pQCT. Both raloxifene and ethynyl estradiol had beneficial effects on serum lipids, producing 50% reduction of cholesterol at 0.1 mg/kg/day raloxifene and 80% reduction with 0.01 m/kg/day ethynyl estradiol. However, raloxifene up to 10 mg/kg/day had little effect on uterine weight, whereas 0.01 mg/kg/day ethynyl estradiol increased uterine wet weight by 300%. These data show that although ethynyl estradiol is 25 times more potent than **raloxifene** in preventing **bone loss** due to ovariectomy in an aged rat model, raloxifene may have advantages over hormone replacement in the treatment of bone loss due to estrogen deficiency.

L45 ANSWER 27 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:367761 HCAPLUS
DOCUMENT NUMBER: 122:123961
TITLE: Parathyroid hormone and raloxifene for increasing bone mass.
INVENTOR(S): Hock, Janet Mary
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 7 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 635270	A1	19950125	EP 1994-305238	19940718 <--
EP 635270	B1	20000301		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
ZA 9405249	A	19960118	ZA 1994-5249	19940718 <--
AT 189959	E	20000315	AT 1994-305238	19940718 <--
ES 2142380	T3	20000416	ES 1994-305238	19940718 <--
PT 635270	T	20000731	PT 1994-305238	19940718 <--
IL 110350	A1	20020210	IL 1994-110350	19940718 <--
CZ 289648	B6	20020313	CZ 1994-1733	19940718 <--
CA 2128376	AA	19950123	CA 1994-2128376	19940719 <--
NO 9402708	A	19950123	NO 1994-2708	19940719 <--
AU 9467577	A1	19950202	AU 1994-67577	19940719 <--
AU 686628	B2	19980212		
JP 07069920	A2	19950314	JP 1994-166809	19940719 <--
RU 2155042	C2	20000827	RU 1994-27680	19940719 <--
BR 9402902	A	19950411	BR 1994-2902	19940721 <--
HU 67945	A2	19950529	HU 1994-2157	19940721 <--
HU 219382	B	20010328		
CN 1105882	A	19950802	CN 1994-108159	19940721 <--
CN 1105577	B	20030416		
US 5510370	A	19960423	US 1995-400436	19950306 <--
HK 1013800	A1	20001124	HK 1998-115198	19981223 <--
GR 3033492	T3	20000929	GR 2000-401189	20000524 <--

PRIORITY APPLN. INFO.: US 1993-96480 A 19930722 <--

AB The s.c. sequential, concurrent, or simultaneous administration of 1-34-human parathyroid hormone (8 μg/100 g/day) and raloxifene (0.3 mg/100g/day) to ovariectomized rats increased bone mass and was effective in treating bone loss.

L45 ANSWER 28 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:333200 HCAPLUS
DOCUMENT NUMBER: 122:96017
TITLE: Antiestrogens inhibit in vitro bone resorption stimulated by 1,25-dihydroxyvitamin D3 and the vitamin D3 analogs EB1089 and KH1060
AUTHOR(S): Vink-van Wijngaarden, Trudy; Birkenhaeger, Jan C.; Kleinekoort, Wendy M. C.; van den Bernd, Gert-Jan C. M.; Pols, Huibert A. P.; van Leeuwen, P. T. M.
CORPORATE SOURCE: Dep. Internal Med. III, Erasmus Univ. Med. Sch., Rotterdam, 3000 DR, Neth.
SOURCE: Endocrinology (**1995**), 136(2), 812-15
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1,25-Dihydroxyvitamin D3 (1,25-(OH)2D3) has been shown to inhibit breast cancer cell growth both in vitro and in vivo. A major drawback is that high doses of 1,25-(OH)2D3 are needed which may result in undesirable side effects like the development of hypercalcemia and an increased risk of bone metastases due to the stimulation of bone resorption by 1,25-(OH)2D3. Several newly developed 1,25-(OH)2D3 analogs have a reduced calcemic activity, but their effects on bone resorption have not yet been examined Presently, the antiestrogen tamoxifen is the most important endocrine therapy for breast cancer. Recent studies have demonstrated the benefit of the combination tamoxifen and 1,25-(OH)2D3/analogs for the inhibition of breast cancer cell growth. Besides inhibition of breast cancer growth tamoxifen appeared to have beneficial effects on bone. The purpose of the present study was to investigate the effect of tamoxifen on 1,25-(OH)2D3- and analogs (EB 1089 and KH 1060)-stimulated bone resorption in an in vitro model. Bone resorption was stimulated by 1,25-(OH)2D3 and analogs

in a dose-dependent manner with KH 1060 and EB 1089 being more potent than 1,25-(OH)2D3. Tamoxifen caused a strong dose-dependent inhibition (70% at 10 μM) of 1,25-(OH)2D3- and EB 1089-stimulated bone resorption. KH 1060-stimulated bone resorption was also inhibited by tamoxifen but to a lesser extent (36%). Also the pure antiestrogen ICI164,384 but not 17β-estradiol inhibited 1,25-(OH)2D3-stimulated bone resorption. Together, this study demonstrates that tamoxifen considerably reduces 1,25-(OH)2D3/analogs-stimulated bone resorption and therefore may be useful to reduce the risk of bone metastases. This together with the observed beneficial effects on breast cancer cell growth indicates that tamoxifen together with 1,25-(OH)2D3/analogs is an interesting combination for the treatment of breast cancer. The mechanism of the bone resorption inhibitory action is not yet known but seems to be independent of the estrogen pathway.

L45 ANSWER 29 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:646209 HCAPLUS
DOCUMENT NUMBER: 121:246209
TITLE: In the ovariectomized rat, tamoxifen conserves bone similarly in parathyroid-intact and parathyroidectomized animals
AUTHOR(S): Goulding, A.; Gold, E.
CORPORATE SOURCE: Department Medicine, University Otago, Dunedin, N. Z.
SOURCE: Bone (New York, NY, United States) (**1994**), 15(5), 497-503
CODEN: BONEDL; ISSN: 8756-3282
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To examine the ability of tamoxifen (TAM) to conserve bone in the estrogen-deficient ovariectomized (OVX) rat in the presence and absence of parathyroid hormone (PTH) six groups of rats with 45Ca-labeled bones were studied for 12 wk. Rats were OVX, parathyroidectomized (PTX), or given sham operations and treated with TAM (10 mg/kg body weight/wk s.c.) or TAM-vehicle. Treatments were: group 1 = Sham-OVX; group 2 = Sham-OVX + TAM; group 3 = OVX; group 4 = OVX + TAM; group 5 = OVX + PTX; and group 6 = OVX + PTX + TAM. To monitor bone resorption serial measurements of urinary hydroxyproline and 45Ca excretion were made during the study. Ovariectomy raised these markers of bone breakdown and caused significant osteopenia, whereas TAM prevented ovariectomy increasing urinary hydroxyproline or 45Ca and conserved bone. Final total body calcium values (TBCa) in groups 1-6, resp., were (mg ± SD): 3240 ± 300; 3260 ± 289; 2750 ± 231; 3212 ± 312; 2742 ± 199; and 3387 ± 252. Thus ovariectomy reduced TBCa similarly in the presence and absence of the parathyroids ($p < 0.001$). In contrast TAM fully protected both PT-intact and PTX rats from the osteopenic effect of ovariectomy, despite the fact that PTX rats had a lower rate of bone turnover than PT-intact rats. However, TAM-treated OVX rats had shorter femora than OVX rats given TAM-vehicle, suggesting that TAM suppresses growth of the long bones to some degree in estrogen-deficient animals. We conclude that, in the rat, TAM conserves the skeleton from estrogen-deficiency bone loss independently of changes in PT function. Estrogen-deficiency bone loss is no greater in rats with a high rate of PTH-mediated bone breakdown than in rats with a low rate of PTH-mediated bone turnover.

L45 ANSWER 30 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:525143 HCAPLUS
DOCUMENT NUMBER: 121:125143
TITLE: Dual-energy X-ray absorptiometry of raloxifene effects on the lumbar vertebrae and femora of ovariectomized rats

AUTHOR(S): Sato, Masahiko; McClintock, Cindy; Kim, John; Turner, Charles H.; Bryant, Henry U.; Magee, David; Slemenda, Charles W.
CORPORATE SOURCE: Lilly Res. Lab., Dep. Endocr. Res., Indianapolis, IN, USA
SOURCE: Journal of Bone and Mineral Research (**1994**), 9(5), 715-24
CODEN: JBMREJ; ISSN: 0884-0431
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new potential therapeutic agent for postmenopausal **osteoporosis**, **raloxifene**, previously known as keoxifene, was evaluated by x-ray densitometry and more traditional techniques in quantitating the short-term (4-5 wk) effects of ovariectomy on bones from 6-mo-old rats. A Hol. QDR 1000/W and, to a limited extent, a Lunar DPXL, was used to quantitate ovariectomy, estrogen replacement, and raloxifene effects on vertebrae, femora, and tibiae. Both instruments performed well with precisions of 1.6% (Hol.) and 0.9% (Lunar) for anesthetized rats, which improved to 0.4% (Hol.) and 0.5% (Lunar) when the same rats were frozen. The lumbar vertebrae L1-4 showed a 12% decrease in bone mineral d. 4 wk after ovariectomy, compared with a 9% decrease for femora. Tibiae were also examined, but edge-detection problems prevented reproducible anal. of this site in vivo. The decrease in bone mineral d. postovariectomy, especially for femora, was found to include both an increase in the projected area and a slight but not significant decrease in the bone mineral content of L1-4 and femora. These changes in d. parameters of femora were supported by a decrease in dry weight and volume and a marginal increase in the second moment of inertia I for the identical femora examined ex vivo. Examination of individual lumbar vertebrae L1-5 suggested that the bone mineral d. of L3 changes most dramatically in response to ovariectomy, but present techniques lack the spatial resolution and precision to quantitate bone changes reliably in individual vertebrae. 17β-Estradiol administered at 100 μg/kg/day s.c. inhibited ovariectomy effects on L1-4 bone mineral d., femoral moment of inertia, dry weight, and volume and to a lesser extent, femoral bone mineral d. A nonsteroidal compound, raloxifene HCl, at 1 mg/kg/day per os, had bone effects and effects on body weight that were largely indistinguishable from those of 17β-estradiol; however, raloxifene did not produce the uterotrophic effects observed with estrogen. The half-maximal efficacious dose of raloxifene on L1-4 bone mineral d. was between 0.1 and 1.0 mg/kg/day per os. These data show that dual-energy x-ray absorptiometry compares favorably with traditional methods in quantitating bone changes caused by ovariectomy in small rodents, that L1-4 is a more sensitive region than whole femora in evaluating the effect of estrogen deficiency on **bone loss**, and the **raloxifene** may have promise as a treatment for conditions characterized by excessive bone loss after ovariectomy.

L45 ANSWER 31 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:418076 HCAPLUS
DOCUMENT NUMBER: 121:18076
TITLE: Pharmaceutical compositions containing benzothiophenes for treatment of osteoporosis
INVENTOR(S): Black, Larry J.; Cullinan, George J.
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Can. Pat. Appl., 51 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
CA 2101356	AA	19940129	CA 1993-2101356	19930727	<--
CA 2101356	C	19981117			
ZA 9305283	A	19950123	ZA 1993-5283	19930721	<--
NZ 314686	A	20000728	NZ 1993-314686	19930721	<--
NO 9302650	A	19940131	NO 1993-2650	19930722	<--
IL 106450	A1	19991231	IL 1993-106450	19930722	<--
CZ 281913	B6	19970312	CZ 1993-1498	19930723	<--
EP 584952	A1	19940302	EP 1993-305860	19930726	<--
EP 584952	B1	19970502			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
HU 65707	A2	19940728	HU 1993-2163	19930726	<--
HU 219233	B	20010328			
AT 152351	E	19970515	AT 1993-305860	19930726	<--
EP 781555	A1	19970702	EP 1997-200262	19930726	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
ES 2102602	T3	19970801	ES 1993-305860	19930726	<--
EP 1438957	A1	20040721	EP 2004-101615	19930726	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE					
AU 9344221	A1	19940203	AU 1993-44221	19930727	<--
AU 658075	B2	19950330			
BR 9303013	A	19940216	BR 1993-3013	19930727	<--
RU 2104697	C1	19980220	RU 1993-48466	19930727	<--
KR 161300	B1	19981201	KR 1993-14329	19930727	<--
PL 177348	B1	19991029	PL 1993-299814	19930727	<--
CN 1088205	A	19940622	CN 1993-117097	19930728	<--
CN 1054742	B	20000726			
JP 06199665	A2	19940719	JP 1993-185965	19930728	<--
JP 2749247	B2	19980513			
JP 10114656	A2	19980506	JP 1997-258937	19930728	<--
JP 3162662	B2	20010508			
RO 113212	B1	19980529	RO 1993-1066	19930728	<--
US 5393763	A	19950228	US 1994-180522	19940112	<--
US 5457117	A	19951010	US 1994-329396	19941026	<--
US 5534527	A	19960709	US 1995-422096	19950414	<--
NZ 504611	A	20050729	NZ 2000-504611	20000518	<--
PRIORITY APPLN. INFO.:			US 1992-920933	A 19920728	<--
			EP 1993-305860	A3 19930726	<--
			EP 1997-200262	A3 19930726	<--
			JP 1993-185965	A3 19930728	<--
			US 1994-180522	A3 19940112	<--
			US 1994-329396	A1 19941026	<--

OTHER SOURCE(S): MARPAT 121:18076

AB Pharmaceutical compns. containing benzothiophenes are used for treatment or preventing osteoporosis by inhibiting the loss of bone. These compds. can be used without the associated adverse effects of estrogen therapy, and thus are effective in the prevention or treatment of osteoporosis. Ovariectomized rats were administered 1.00 mg/kg oral raloxifene (I) for 35 days and then sacrificed. The bone d. and uterine weight was 201 and 199 as compared to 171 mg/cm/cm and 127 mg for the controls. A capsule contained I.HCl 1, starch 112, starch flowable powder 225.3, and silicone fluid 350 cSt 1.7 mg.

L45 ANSWER 32 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:290331 HCAPLUS
DOCUMENT NUMBER: 120:290331
TITLE: Mechanism of action of estrogen on cancellous bone balance in tibiae of ovariectomized growing rats:

inhibition of indices of formation and resorption
AUTHOR(S): Turner, Russell T.; Evans, Glenda L.; Wakley, Glenn K.
CORPORATE SOURCE: Dep. Orthop. Surg., Mayo Found., Rochester, MN, USA
SOURCE: Journal of Bone and Mineral Research (**1993**), 8(3), 359-66
CODEN: JBMREJ; ISSN: 0884-0431
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ovariectomy results in cancellous osteopenia in rat long bones, a condition that is prevented by treatment with estrogens. The purpose of these studies was to clarify the effects of estrogen on cancellous bone turnover using dynamic bone histomorphometry. Treatment of ovariectomized rats with DES reduced the mineral apposition rate, double-label perimeter, osteoblast number, suggesting that the hormone had inhibitory effects on bone formation as well as bone resorption. However, the authors could not estimate the bone formation rate because of rapid resorption of tetracycline-labeled bone in the ovariectomized rat. The magnitude of loss was documented by a time course study: 58% of the tetracycline initially incorporated into the secondary spongiosa of the tibial metaphysis was resorbed after 11 days and 89% was resorbed after 22 days. Similarly, cancellous bone area was decreased by 67% after 11 days and by 88% after 22 days. Administration of either DES or tamoxifen (TAM) dramatically reduced resorption of tetracycline as well as the decrease in cancellous bone area. These results demonstrate that (1) estrogen prevents osteopenia in ovariectomized (OVX) rats, in part by inhibiting bone turnover, (2) TAM is an estrogen agonist on bone resorption, and (3) resorption of tetracycline-labeled bone leads to serious underestimation of the bone formation rate in OVX rats.

L45 ANSWER 33 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:236405 HCAPLUS
DOCUMENT NUMBER: 120:236405
TITLE: **Raloxifene** (LY139481 HCl) prevents **bone loss** and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats
AUTHOR(S): Black, Larry J.; Sato, Masahiko; Rowley, Ellen R.; Magee, David E.; Bekele, Aster; Williams, Daniel C.; Cullinan, George J.; Bendele, Raymond; Kauffman, Raymond F.; et al.
CORPORATE SOURCE: Dep. Skeletal Dis. Res., Eli Lilly Co., Indianapolis, IN, 46285, USA
SOURCE: Journal of Clinical Investigation (**1994**), 93(1), 63-9
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is a medical need for an agent with the pos. effects of estrogen on bone and the cardiovascular system, but without the neg. effects on reproductive tissue. Raloxifene (LY139481 HCl) is a benzothiophene derivative that binds to the estrogen receptor and inhibits the effects of estrogen on the uterus. In an ovariectomized (OVX) rat model the authors investigated the effects of **raloxifene** on **bone loss** (induced by estrogen deficiency), serum lipids, and uterine tissue. After oral administration of raloxifene for 5 wk (0.1-10 mg/kg per d) to OVX rats, bone mineral d. in the distal femur and proximal tibia was greater than that observed in OVX controls (ED50 of 0.03-0.3 mg/kg). Serum cholesterol was lower in the raloxifene-treated animals, which had a minimal ED of 0.1 mg/kg and an approx. oral ED50 of 0.2 mg/kg. The effects of raloxifene on bone and serum cholesterol were comparable to

those of a 0.1-mg/kg per d oral dose of ethynyl estradiol. Raloxifene diverged dramatically from estrogen in its lack of estrogenic effects on uterine tissue. Ethynyl estradiol produced a marked elevation in a number of uterine histol. parameters (e.g., epithelial cell height, stromal eosinophilia). These data suggest that raloxifene has promise as an agent with beneficial bone and cardiovascular effects in the absence of uterine effects.

L45 ANSWER 34 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:509317 HCAPLUS
DOCUMENT NUMBER: 119:109317
TITLE: Effects of onapristone, tamoxifen and ICI 182780 on uterine prostaglandin production and luteal function in nonpregnant guinea pigs
AUTHOR(S): Poyser, N. L.
CORPORATE SOURCE: Med. Sch., Univ. Edinburgh, Edinburgh, EH8 9JZ, UK
SOURCE: Journal of Reproduction and Fertility (**1993**), 98(1), 307-12
CODEN: JRPFA4; ISSN: 0022-4251
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Onapristone (a progesterone antagonist) or ICI 182780 (an estrogen antagonist) administered to guinea-pigs on days 11-14 of the cycle significantly reduced uterine PGF2α output on day 15. Concns. of progesterone in plasma of onapristone-treated and ICI 182780-treated guinea pigs were still high on day 15 indicating that luteal regression had been prevented. These findings indicate that progesterone and estradiol are necessary for increased PGF2α production by the uterus towards the end of the cycle, and support the hypothesis that estradiol acting on a progesterone-primed uterus is the physiol. stimulus for increased uterine PGF2α synthesis and release in guinea-pigs. The capacity of the endometrium to synthesize PGF2α on day 15 was reduced by treatment with ICI 182780 and, unexpectedly, by treatment with onapristone, indicating that onapristone may also be antagonizing the release or action of estradiol in some way. Tamoxifen was an agonist in guinea-pigs since it induced vaginal opening. It has no inhibitory effect on uterine PGF2α output and did not delay luteal regression when administered between days 11 and 14 of the cycle. However, it redirected PG synthesis in homogenates of endometrium and myometrium from PGI2 (as indicated by 6-keto-PGF1α) to PGF2α. The output of 6-keto-PGF1α from the uterus of day 15 guinea-pigs was reduced following **tamoxifen** treatment, but the high output of **PGF2α** from the uterus was not affected.

L45 ANSWER 35 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:74231 HCAPLUS
DOCUMENT NUMBER: 118:74231
TITLE: Prostaglandin E2 prevents ovariectomy-induced cancellous bone loss in rats
AUTHOR(S): Ke, Hua Zhu; Li, Mei; Jee, Webster S. S.
CORPORATE SOURCE: Sch. Med., Univ. Utah, Salt Lake City, UT, USA
SOURCE: Bone and Mineral (**1992**), 19(1), 45-62
CODEN: BOMIET; ISSN: 0169-6009
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Daily administration of PGE2 (1 or 6 mg/kg) to ovariectomized rats for 90 days decreased bone tumors and increased bone formation parameters, resulting in a pos. bone balance that prevented bone loss at the lower dose and added extra bone at the higher concentration This supported the use of

bone stimulation agents in preventing estrogen depletion bone loss (post menopausal osteoporosis).

L45 ANSWER 36 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:74230 HCAPLUS
DOCUMENT NUMBER: 118:74230
TITLE: Prostaglandin E2 alleviates cyclosporin A-induced bone loss in the rat
AUTHOR(S): Katz, I. A.; Jee, W. S. S.; Joffe, I. I.; Stein, B.; Takizawa, M.; Jacobs, T. W.; Setterberg, R.; Lin, B. Y.; Tang, L. Y.; et al.
CORPORATE SOURCE: Div. Endocrinol. Metab., Albert Einstein Med. Cent., Philadelphia, PA, USA
SOURCE: Journal of Bone and Mineral Research (**1992**), 7(10), 1191-200
CODEN: JBMREJ; ISSN: 0884-0431
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of PGE2 on cyclosporin A-induced alterations in circulating markers of bone mineral metabolism (bone gla protein, parathormone, and 1,25-dihydroxyvitamine D) and proximal tibial trabecular bone histomorphometry were studied in rats. The concurrent administration of PGE2 with cyclosporin A alleviated the altered bone mass induced by cyclosporin alone by adding a significant amount of addnl. bone.

L45 ANSWER 37 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:645627 HCAPLUS
DOCUMENT NUMBER: 117:245627
TITLE: droloxifene in treatment of bone diseases
INVENTOR(S): Niikura, Kazuaki; Nakajima, Yoshimitsu; Notsu, Yoshitada; Ono, Ryuji; Nakayama, Osamu
PATENT ASSIGNEE(S): Klinge Pharma GmbH, Germany
SOURCE: Eur. Pat. Appl., 5 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 509317	A2	19921021	EP 1992-105595	19920401 <--
EP 509317	A3	19930303		
EP 509317	B1	19941117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
JP 04312526	A2	19921104	JP 1991-166944	19910409 <--
ES 2064130	T3	19950116	ES 1992-105595	19920401 <--
AU 9213994	A1	19921015	AU 1992-13994	19920402 <--
AU 648154	B2	19940414		
CA 2065093	AA	19921010	CA 1992-2065093	19920403 <--
CA 2065093	C	19951003		
KR 196810	B1	19990615	KR 1992-5743	19920407 <--
ZA 9202527	A	19921230	ZA 1992-2527	19920408 <--
US 5254594	A	19931019	US 1992-865106	19920408 <--
PRIORITY APPLN. INFO.:			JP 1991-166944 A	19910409 <--

AB Droloxifene and its salts are used in treatment of bone diseases, e.g. osteoporosis. Thus, ovariectomized rats showed an 84% recovery of bone d. after 4 wk administration of droloxifene citrate (5 mL 0.5% suspension/kg/day orally for 4 wk). Tablets were prepared, each containing droloxifene citrate 10, lactose 119, low-substituted

hydroxypropylcellulose 25, PVP 5, and Mg stearate 1 mg.

L45 ANSWER 38 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:441227 HCAPLUS
DOCUMENT NUMBER: 117:41227
TITLE: Effect of exogenously applied prostaglandin E2 on alveolar bone loss - histometric analysis
AUTHOR(S): Miyauchi, Mutsumi; Ijuhin, Naokuni; Nikai, Hiromasa; Takata, Takashi; Ito, Hiroshi; Ogawa, Ikuko
CORPORATE SOURCE: Sch. Dent., Hiroshima Univ., Hiroshima, Japan
SOURCE: Journal of Periodontology (**1992**), 63(5), 405-11
CODEN: JOPRAJ; ISSN: 0022-3492
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PGE2 on alveolar bone resorption was examined in 8-wk-old Wistar rats by histometric anal. PGE2 (1 mg/mL) topically applied to gingival sulcus induced a marked increase in osteoclasts. The number of osteoclasts increased progressively and reached a maximum at 12 h. Ultrastructurally, these osteoclasts were in active form with well developed ruffled borders and clear zones. The changes in nos. of osteoclasts after application of various concns. of PGE2 were dose-dependent (0.001 to 1.0 mg/mL), but higher concns. of PGE2 (2 mg/mL) were less effective. In addition, the number of osteoclasts in groups treated with both PGE2 and endotoxin was higher than those that received PGE2 only. These results indicate that bone resorption caused by PGE2 depends on activation and increase of osteoclasts, and suggests that endogenous PGE2 production by host cells stimulated by plaque-associated bacterial endotoxin may be an important pathogenetic factor in periodontal disease.

L45 ANSWER 39 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:401656 HCAPLUS
DOCUMENT NUMBER: 117:1656
TITLE: Prostaglandin E2 prevents disuse-induced cortical bone loss
AUTHOR(S): Jee, W. S. S.; Akamine, T.; Ke, H. Z.; Li, X. J.; Tang, L. Y.; Zeng, Q. Q.
CORPORATE SOURCE: Sch. Med., Univ. Utah, Salt Lake City, UT, 84112, USA
SOURCE: Bone (New York, NY, United States) (**1992**), 13(2), 153-9
CODEN: BONEDL; ISSN: 8756-3282
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The object of this study was to determine whether PGE2 can prevent disuse (underloaded)-induced cortical bone loss as well as add extra bone to underloaded bones. Thirteen-month-old retired female Sprague-Dawley breeders served as controls or were subjected to simultaneous right hindlimb immobilization by bandaging and daily s.c. doses of 0, 1, 3, or 6 mg PGE2/kg/d for two and six weeks. Histomorphometric analyses were performed on double-fluorescent labeled undecalcified tibial shaft sections (proximal to the tibiofibular junction). Disuse-induce cortical bone loss occurred by enlarging the marrow cavity and increasing intracortical porosity. PGE2 treatment of disuse shafts further increased intracortical porosity above that in disuse alone controls. This bone loss was counteracted by enhancement of periosteal and corticoendosteal bone formation. Stimulation of periosteal and corticoendosteal bone formation slightly enlarged the total tissue (cross-sectional) area and inhibited marrow cavity enlargement. These PGE2-induced activities netted the same percentage of cortical bone with a different distribution than the beginning and age-related controls. These findings indicate the .

PGE2-induced increase in bone formation compensated for the disuse and **PGE2**-induced **bone loss**, and thus prevented immobilization-induced bone loss.

L45 ANSWER 40 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:248381 HCAPLUS
DOCUMENT NUMBER: 116:248381
TITLE: **Tamoxifen** prevents **bone loss** in ovariectomized mice
AUTHOR(S): Broulik, P. D.
CORPORATE SOURCE: Fac. Med., Charles Univ., Prague, 128 21, Czech.
SOURCE: Endocrine Regulations (**1991**), 25(4), 217-19
CODEN: EREGE3; ISSN: 1210-0668
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bone d. and mineral content of the femora were decreased in ovariectomized mice compared with intact control animals. Tamoxifen treated ovariectomized mice did not develop a decrease either in the bone d. or in calcium and phosphate content of the femora which were observed in ovariectomized mice. In addition, the weight of uterus in tamoxifen-treated ovariectomized mice was the same as in intact controls. Thus, tamoxifen administered in vivo prevented the loss of bone mineral and uterus weight in ovariectomized mice and thus showing true estrogen like activity.

L45 ANSWER 41 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:76566 HCAPLUS
DOCUMENT NUMBER: 116:76566
TITLE: A comparative study of the actions of tamoxifen, estrogen and progesterone in the ovariectomized rat
AUTHOR(S): Kalu, D. N.; Salerno, E.; Liu, C. C.; Echon, R.; Ray, M.; Garza-Zapata, M.; Hollis, B. W.
CORPORATE SOURCE: Health Sci. Cent., Univ. Texas, San Antonio, TX, 78284-7756, USA
SOURCE: Bone and Mineral (**1991**), 15(2), 109-23
CODEN: BOMIET; ISSN: 0169-6009
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study was undertaken to examine the sep. and combined effects of tamoxifen (T), estrogen (E2), and progesterone (P) treatment on ovariectomized (Ooph) rats. The animals were treated for 40 days. Ovariectomy reduced cancellous bone volume at the proximal tibia by 50%. Estradiol treatment completely prevented the bone loss and further increased bone volume 77% over the level for the control group. Tamoxifen also prevented the ovariectomy-induced bone loss, but reduced the increase in cancellous bone induced by estradiol. In the ovariectomized rats, cancellous bone apposition rate increased 23%. This increase was suppressed 63% by estradiol, and only 18% by tamoxifen. Tamoxifen suppressed the inhibitory effect of estradiol on cancellous bone appositon rate. In contrast, the effect of progesterone treatment was only marginal. These findings indicate that the action of tamoxifen on bone is influenced by the ambient level of circulating estradiol, such that in estrogen deficiency, tamoxifen has a weak estrogen against action on bone, and in the presence of estrogen it has antiestrogen actions, with the dose level and mode of administration employed. These conclusions have implications for the use of tamoxifen in the treatment of pre- and postmenopausal women.

L45 ANSWER 42 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:527849 HCAPLUS
DOCUMENT NUMBER: 115:127849

TITLE: Bone cell responsiveness to transforming growth factor β, parathyroid hormone, and prostaglandin E2 in normal and postmenopausal osteoporotic women
AUTHOR(S): Lomri, Abderrahim; Marie, Pierre J.
CORPORATE SOURCE: Hop. Lariboisiere, Paris, 75010, Fr.
SOURCE: Journal of Bone and Mineral Research (**1990**), 5(11), 1149-55
CODEN: JBMREJ; ISSN: 0884-0431
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Primary cultures of bone cells with osteoblastic characteristics were obtained by migration from the trabecular bone surface in osteoporotic postmenopausal women with high or low bone formation as evaluated histomorphometrically by the extent of double tetracycline labeled surface (DLS). Control bone cells were obtained under identical conditions from eight normal age-matched postmenopausal women. Cell replication as evaluated by [3H]thymidine into DNA was 3.4-fold lower in the low DLS group compared to the high DLS group. Treatment of quiescent bone cells with transforming growth factor β (TGF-β) (0.5-1 ng/mL) for 24 h stimulated DNS synthesis in osteoblastic cells from normal women and in bone cells from osteoporotic patients with low or high DLS, indicating a normal responsiveness to TGF-β in these patients. Basal cAMP levels and the cAMP accumulation in response to (1-34)-human parathyroid hormone (PTH) were similar in bone cells from patients with low or high DLS and were not different from normal values. PGE2 (24 h) produced a dose-related biphasic effect on DNA synthesis in bone cells from both normal and osteoporotic women. At low concentration (10-11 M) PGE2 increased DNS synthesis whereas at higher concentration (10-7 M) it was inhibitory. The cAMP production was increased by PGE2 at doses that inhibited DNA synthesis. The responsiveness to PGE2 was not different in normal bone cells and in cells from osteoporotic women with low and high DLS. Apparently the reduced bone cell proliferative capacity in osteoporotic postmenopausal women with low bone formation does not result from a lower than normal responsiveness to TGF-β, PTH, and PGE2.

L45 ANSWER 43 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:192124 HCAPLUS
DOCUMENT NUMBER: 112:192124
TITLE: Effects of clomiphene and tamoxifen in vivo on the bone-resorbing effects of parathyroid hormone and of high oral doses of calcitriol (1,25-dihydroxyvitamin D3) in rats with intact ovarian function consuming low calcium diet
AUTHOR(S): Goulding, A.; Gold, E.; Fisher, L.
CORPORATE SOURCE: Med. Sch., Univ. Otago, Dunedin, N. Z.
SOURCE: Bone and Mineral (**1990**), 8(3), 185-93
CODEN: BOMIET; ISSN: 0169-6009
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two expts. were undertaken to study the abilities of clomiphene citrate (20 mg/kg/wk, s.c.) and tamoxifen (20 mg/kg/wk, s.c.) to slow bone resorption mediated by endogenous parathyroid hormone (PTH) and exogenous calcitriol (1,25(OH)2D3) in vivo in rats with intact ovarian function. Groups of rats with 45C-labeled bones were fed a low-Ca (0.01% Ca) diet to stimulate secretion of PTH. Neither clomiphene nor tamoxifen slowed the mobilization of 45Ca from femoral bone or prevented the reduction in bone Ca induced by feeding this diet. Moreover these drugs did not depress the urinary excretion of 45Ca or hydroxyproline. These observations indicated that clomiphene and tamoxifen did not inhibit PTH-mediated bone

resorption. Administering 1,25(OH)2D3 (50 ng/day) orally for 14 days raised plasma Ca, increased urinary 45Ca and its specific activity, and decreased femur 45Ca: all these responses were similar in animals receiving 1,25(OH)2D3 alone and 1,25(OH)2D3 with clomiphene or tamoxifen. The femur 45Ca values (dpm + 10-3) were: placebo, 1901; 1,25(OH)2D3, 164; tamoxifen + 1,25(OH)2D3, 1664. Thus, neither clomiphene nor tamoxifen prevented 1,25(OH)2D3-mediated bone resorption in vivo in the rat.

L45 ANSWER 44 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:433304 HCAPLUS
DOCUMENT NUMBER: 111:33304
TITLE: Effects of antirheumatic drugs on the interleukin 1α-induced synthesis and activation of proteinases in articular cartilage explants in culture
AUTHOR(S): Arsenis, C.; McDonnell, J.
CORPORATE SOURCE: Pharm. Div., Ciba-Geigy Corp., Summit, NJ, 07901, USA
SOURCE: Agents and Actions (**1989**), 27(3-4), 261-4
CODEN: AGACBH; ISSN: 0065-4299
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three human cytokines (interleukin-1α and interleukin-1β and tumor necrosis factor-α), added into the medium of bovine or rabbit articular cartilage explant cultures, stimulated the synthesis and activation of various proteinases. Proteoglycan degradation was correlated with the proteinase stimulation. Several antirheumatic drugs were tested in similar tissue culture system as potential inhibitors of the interleukin-1α mediated stimulation of proteinase and PGE2 syntheses. Arteparon, dexamethasone, ibuprofen, indomethacin, levamisole, naproxen, phenylbutazone, prednisolone, piroxicam, rumalon, tamoxifen, and diclofenac were essentially ineffective in inhibiting the interleukin 1α-mediated induction of proteinase synthesis and sulfated glycosaminoglycan release, although some of them inhibited PGE2 synthesis. Two antimalarial drugs showed some inhibition, but only at higher concns.

L45 ANSWER 45 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:143689 HCAPLUS
DOCUMENT NUMBER: 108:143689
TITLE: Tamoxifen inhibits osteoclast-mediated resorption of trabecular bone in ovarian hormone-deficient rats
AUTHOR(S): Turner, Russell T.; Wakley, Glenn K.; Hannon, Kathleen S.; Bell, Norman H.
CORPORATE SOURCE: Dep. Physiol. Pharmacol., Loma Linda Univ., Loma Linda, CA, 92354, USA
SOURCE: Endocrinology (**1988**), 122(3), 1146-50
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the nonsteroidal antiestrogen tamoxifen were determined on trabecular bone mass in the proximal tibial metaphysis of intact and ovariectomized rats. Rats were ovariectomized at the beginning of the study. On day 7 of the study, 5-mg slow-release pellets of tamoxifen or placebo were implanted s.c. All of the rats were killed on day 28 of the experiment Sections of the proximal tibial metaphysis were stained for acid phosphatase and evluated histomorphometrically. Ovariectomy resulted in marked loss of bone. Compared to the values in sham-operated animals, the trabecular bone at a sampling site in the secondary spongiosa of ovariectomized rats was reduced by >60%, the length of trabecular bone surface covered by osteoclasts was increased by 563%, the percentage of trabecular bone surface covered by osteoclasts was increased by 567%, the

mean osteoclast size was increased by 84%, and the number of nuclei per osteoclast was increased by 38%. In contrast, treatment of ovariectomized rats for 3 wk with tamoxifen restored the histomorphometric measurements to values comparable to those in sham-operated animals. 17β-Estradiol increased trabecular bone fractional area in ovariectomized and sham-operated rats, and administration of tamoxifen to estrogen-treated, ovariectomized, and sham-operated animals produced a further increase in trabecular bone. In summary, (1) ovariectomy resulted in large increases in both the number and activity of osteoclasts, (2) the increased bone resorption associated with ovariectomy produced a net loss of trabecular bone, and (3) treatment of ovariectomized rats with tamoxifen prevented these skeletal changes. Evidently, in the rat, tamoxifen mimics the effects of estrogen on trabecular bone at concns. that are not uterotropic.

L45 ANSWER 46 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:69162 HCAPLUS
DOCUMENT NUMBER: 108:69162
TITLE: Effects of anti-estrogens on bone in castrated and intact female rats
AUTHOR(S): Jordan, V. Craig; Phelps, Erik; Lindgren, J. Urban
CORPORATE SOURCE: Clin. Cancer Cent., Univ. Wisconsin, Madison, WI, 53792, USA
SOURCE: Breast Cancer Research and Treatment (**1987**), 10(1), 31-5
CODEN: BCTRD6; ISSN: 0167-6806
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the antiestrogens tamoxifen and keoxifene on the bone d. of intact and ovariectomized female rats were determined after 4 mo of therapy. The antiestrogen did not cause a decrease in bone d. in intact animals, although uterine wet weight did decrease. Ovariectomy caused an increase in body weight (25%) and a decrease in femur d. Antiestrogens did not further decrease the bone d. of ovariectomized rats, but rather helped to maintain bone d. Antiestrogens as well as estrogen (oral estradiol benzoate 25 μg daily) helped to maintain bone d. in the range observed for the intact rats, but inhibited estrogen stimulation of uterine weight These contrasting pharmacol. actions of antiestrogens suggest that patients receiving long-term adjuvant tamoxifen therapy for breast cancer should be evaluated to determine whether tamoxifen can retard the development of osteoporosis.

L45 ANSWER 47 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:219385 HCAPLUS
DOCUMENT NUMBER: 104:219385
TITLE: Hormonal effects of PGF2α output by cultures of epithelial and stromal cells in human endometrium
AUTHOR(S): Schatz, Frederick; Markiewicz, Leszek; Gurpide, Erlio
CORPORATE SOURCE: Dep. Obstetr. Gynecol. Reprod. Sci., Mt. Sinai Sch. Med., NY, 10029, USA
SOURCE: Journal of Steroid Biochemistry (**1986**), 24(1), 297-301
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Estradiol [50-28-2] stimulation and progesterone (P) [57-83-0] inhibition of human uterine PGF2α [551-11-1] production were studied using in vitro prepns. of human endometrial tissue and cells. Measurement of PGF2α levels in media from primary cultures of glandular epithelia and stoma revealed that basal outputs were similar in both cell types but were increased by estradiol only in epithelial cells.

Tamoxifen (Tam) and trans-4-**hydroxytamoxifen** (OHTam) did not affect basal **PGF2α** outputs by secretory endometrium in organ culture and by monolayer cultures of epithelial cells, but counteracted the stimulatory effects of estradiol in both systems. The almost pure antiestrogenic activity exhibited by OHTam was at least 10 times greater than that of Tam, suggesting that the estrogen-stimulated increases in uterine PGF2α output are mediated by specific estrogen receptors. Fragments of endometrium also released lipocortin, a phospholipase A2-inhibiting protein believed to mediate inhibitory effects of glucocorticoids on prostaglandin production in several types of cells. Although dexamethasone [50-02-2] increased lipocortin and decreased PGF2α output in secretory endometria in vitro, P inhibited lipocortin and PGF2α output. The mechanism by which P inhibits PGF2α production remains to be elucidated.

L45 ANSWER 48 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:161993 HCAPLUS
DOCUMENT NUMBER: 104:161993
TITLE: Kit for use in the treatment of osteoporosis
INVENTOR(S): Uchtman, Vernon Albert
PATENT ASSIGNEE(S): Procter and Gamble Co., USA
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 162510	A1	19851127	EP 1985-200650	19850425 <--
EP 162510	B1	19910828		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
AT 66608	E	19910915	AT 1985-200650	19850425 <--
CA 1277233	A1	19901204	CA 1985-480203	19850426 <--
AU 8541769	A1	19851107	AU 1985-41769	19850429 <--
AU 584611	B2	19890601		
ZA 8503169	A	19851224	ZA 1985-3169	19850429 <--
DK 8501935	A	19851031	DK 1985-1935	19850430 <--
DK 173735	B1	20010820		
JP 61033117	A2	19860217	JP 1985-93506	19850430 <--
JP 06055675	B4	19940727		
IL 76043	A1	19900429	IL 1985-76043	19850808 <--
US 4812311	A	19890314	US 1986-906859	19860912 <--
EP 381296	A1	19900808	EP 1990-200433	19900223 <--
EP 381296	B1	19941130		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				

PRIORITY APPLN. INFO.:
US 1984-605540 A 19840430 <--
US 1984-684560 A 19841221 <--
EP 1985-200650 A 19850425 <--

AB A regimen kit is described for the treatment of osteoporosis which consists of a bone cell-activating compound (e.g., PO43-, 1,25-dihydroxyvitamin D3, F-, thyroxine, triiodothyronine, PGE2), a bone resorption-inhibiting polyphosphonate, and a nutrient supplement (e.g., Ca, vitamin D), or placebo in sequential administration. For example, patients clin. diagnosed for osteoporosis were treated with 3-8 cycles of regimen in which each cycle consists of 2 tablets (500 mg P each) of phosphate 3 times/day for 3 days, of di-Na ethane-1-hydroxy-1,1-diphosphonate (5 mg/kg/day divided in 3 doses) for 14 days, and remaining 73 days a diet containing ≥1 g Ca/day. All the patients exhibited

significant improvement in osteoporotic conditions.

L45 ANSWER 49 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:62348 HCAPLUS
DOCUMENT NUMBER: 104:62348
TITLE: In vitro inhibition with antiestrogens of estradiol effects on prostaglandin F2α production by human endometrium and endometrial epithelial cells
AUTHOR(S): Schatz, Frederick; Markiewicz, L.; Barg, P.; Gurpide, E.
CORPORATE SOURCE: Dep. Obstet. Gynecol. Reprod. Sci., Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Endocrinology (**1986**), 118(1), 408-12
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ability of antiestrogens to affect PGF2α [551-11-1] output was reevaluated during incubations of human secretory endometrium and in cultures of epithelial cells derived from glands isolated from proliferative and secretory tissues. In these prepns., which respond to estradiol (E2) [50-28-2] with marked elevations in **PGF2**. **alpha**. output, **tamoxifen** and its metabolite trans-4-**monohydroxytamoxifen** acted as virtually pure antagonists, counteracting the E2 effect but failing to influence basal **PGF2**. **alpha**. output. Consistent with its effects on other estrogen-mediated end points, trans-4-monohydroxytamoxifen was at least 10-fold more potent than **tamoxifen**; at a 10-6 M concentration, it inhibited almost completely the stimulatory effect of 10-8 M E2 on **PGF2α** production by both endometrial fragments and monolayers of epithelial cells.

L45 ANSWER 50 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:45971 HCAPLUS
DOCUMENT NUMBER: 104:45971
TITLE: Effects of the antiestrogens **tamoxifen** and clomiphene on **bone resorption** in vitro
AUTHOR(S): Stewart, Pamela J.; Stern, Paula H.
CORPORATE SOURCE: Med. Dent. Sch., Northwest. Univ., Chicago, IL, 60611, USA
SOURCE: Endocrinology (**1986**), 118(1), 125-31
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The in vitro effects of the nonsteroidal antiestrogens tamoxifen (TAM) [10540-29-1] and clomiphene (CLO) [911-45-5] on bone resorption were investigated. TAM (100 μM) and CLO (100 μM) completely blocked parathyroid hormone (PTH) (2 nM)-induced resorption; 10 μM TAM was ineffective in blocking resorption, and 40-50 μM partially inhibited the response. TAM (100 μM) also completely blocked PGE2 (30 nM)- and 1,25-dihydroxyvitamin D3 (0.5 nM)-induced bone resorption. A 16-h pretreatment with TAM blocked subsequent stimulation of resorption by PTH, whereas 3.5- or 7-h pretreatment with antiestrogen was ineffective in blocking the response. Both protein and DNA syntheses were inhibited by continuous treatment (48 h) with the antiestrogens. When antiestrogen-pretreated (16 h) bones were transferred to fresh medium not containing antiestrogen, protein and DNA syntheses recovered to approx. half the control (nonantiestrogen-treated) values within 48 h. Bone resorption was still completely inhibited, however, even though macromol. synthesis had substantially recovered. Thus, mechanisms other than macromol.

synthesis inhibition could be involved in the inhibition of bone resorption by the nonsteroidal antiestrogens TAM and CLO.

L45 ANSWER 51 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:45761 HCAPLUS
DOCUMENT NUMBER: 104:45761
TITLE: Use of a two- or multiphase agent for treating or preventing osteoporosis
INVENTOR(S): Flora, Lawrence
PATENT ASSIGNEE(S): Procter and Gamble Co., USA
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

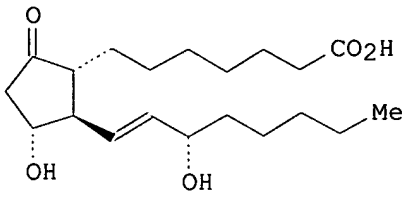
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
DE 3514584	A1	19851031	DE 1985-3514584		19850423	<--
AU 8541484	A1	19851107	AU 1985-41484		19850422	<--
AU 569391	B2	19880128				
BE 902308	A1	19851029	BE 1985-214929		19850429	<--
US 4822609	A	19890418	US 1986-906725		19860912	<--
PRIORITY APPLN. INFO.:			US 1984-605541	A	19840430	<--
			US 1984-684542	A	19841221	<--

AB Osteoporosis is treated by the administration of a bone-cell-activating agent, such as inorg. phosphate, 1,25-dihydroxyvitamin D3, 25-hydroxyvitamin D3, etc., in the 1st stage, followed by the administration of a bone resorption-inhibiting polyphosphonate in the 2nd stage, and the administration of Ca and vitamin D in the 3rd stage. Thus, osteoporotic patients were given phosphate tablets (500 mg P), 3 times per day, for 3 days, followed by the administration of Didronel (5 mg/kg/day) for 14 days. Subsequently, >1 g Ca/day was administered for 45 days. The cycles were repeated 3-8 times. A decrease in the intensity of osteoporosis was observed

L45 ANSWER 52 OF 52 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1983:192484 HCAPLUS
DOCUMENT NUMBER: 98:192484
TITLE: Prostaglandins for osteoporosis therapy
PATENT ASSIGNEE(S): Upjohn Co., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
JP 58029710	A2	19830222	JP 1982-45731		19820324	<--
JP 02016288	B4	19900416				
US 4621100	A	19861104	US 1984-659138		19841009	<--
PRIORITY APPLN. INFO.:			US 1981-247421	A	19810325	<--
			US 1981-305580	A	19810925	<--
			US 1982-353549	A	19820308	<--

GI



I

AB The prostaglandins PGE1 (I) [745-65-3], 2-decarboxy-2-hydroxymethyl-PGE1 [21562-57-2], PGE2 [363-24-6], 15-keto-PGE2 [26441-05-4], 16,16-dimethyl-PGE2 [39746-25-3], 17S,20-dimethyl-6-oxo-PGE1 Me ester [85679-51-2], 17S,20-dimethyl-trans-δ-2-PGE1 [85679-52-3], PGE2 N-methanesulfonylamide [52580-01-5], 9-deoxo-9-methylene-16,16-dimethyl-PGE2 [61263-35-2], 15S-methyl-PGE2 [35700-27-7], 15R-methyl-PGE2 [55028-70-1], 11-deoxy-16,16-dimethyl-PGE2 [53658-98-3], 11-deoxy-11α,16,16-trimethyl-PGE2 [69900-72-7], 6-oxo-11-deoxy-11α,16,16-trimethyl-PGE2 [85679-53-4], 6-oxo-PGE2 [85679-54-5], 6-oxo-PGE1 [67786-53-2], 11-deoxy-15-methyl-PGE1 [54382-28-4], PGE3 [802-31-3], 16,16-difluoro-PGE2 [85679-55-6], and 20-isopropylidene-PGE1 [59896-93-4], with or without steroids, vitamin D [1406-16-2] or its derivs., P-containing agents, parathyroid hormone [9002-64-6], fluoride-containing agents, Ca salts and (or) calcitonin [9007-12-9], are therapeutic and prophylactic agents for osteoporosis. These prostaglandins also are useful in the treatment of fractures, and increase the percentage of success of bone transplantations. The effectiveness of I and PGE2 was tested in dogs.

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                 84449-90-1 OR  10540-29-1 OR 68047-06-3)/RN
L2             7 SEA FILE=REGISTRY ABB=ON  (180915-84-8 OR 180915-78-0 OR
                 180916-16-9 OR 193274-89-4 OR 180916-14-7 OR 180915-86-0 OR
                 180916-15-8)/RN
L3             4 SEA FILE=REGISTRY ABB=ON  (PGD1 OR PGD2 OR PGE2 OR PGE1 OR
                 PGF2 OR PGF2A)/CN
L4             1 SEA FILE=REGISTRY ABB=ON  PGF2A/CN
L5             5 SEA FILE=REGISTRY ABB=ON  L3 OR L4
L6             6 SEA FILE=REGISTRY ABB=ON  L5 OR 195962-24-4/RN
L7         10946 SEA FILE=HCAPLUS ABB=ON  L1 OR ?DROLOXIFENE? OR ?RALOXIFENE?
                 OR ?TAMOXIFEN?
L10           15 SEA FILE=HCAPLUS ABB=ON  L7(20A)(L3 OR L6 OR PGD1 OR PGD2 OR
                 PGE2 OR PGE1 OR PGF2 OR PGF2A OR PGF2A)
L11            3 SEA FILE=HCAPLUS ABB=ON  L10 AND (?BONE?(W)(?LOSS? OR ?RESORP?
                 OR ?LOSE?) OR ?OSTEOPOROS? OR ?PAGET?)
L12           15 SEA FILE=HCAPLUS ABB=ON  L10 OR L11
L14           11 SEA FILE=REGISTRY ABB=ON  L1 OR L2
L15        10991 SEA FILE=HCAPLUS ABB=ON  L14 OR ?DROLOXIFENE? OR ?RALOXIFENE?
                 OR ?TAMOXIFEN?
L20            6 SEA FILE=HCAPLUS ABB=ON  L12 AND (PRD<19960228 OR PD<19960228)
L23        48257 SEA FILE=HCAPLUS ABB=ON  (L6 OR PGD1 OR PGD2 OR PGE2 OR PGE1
                 OR PGF2 OR PGF2A OR PGF2A)
L28          239 SEA FILE=HCAPLUS ABB=ON  L15(3A)(?BONE?(W)(?LOSS? OR ?RESORP?
                 OR ?LOSE?) OR ?OSTEOPOROS? OR ?PAGET?)
L29           37 SEA FILE=HCAPLUS ABB=ON  L28 AND (PRD<19960228 OR PD<19960228)
L36           14 SEA FILE=HCAPLUS ABB=ON  L23(2W)(?BONE?(W)?LOSS? OR ?OSTEOPOROS
                 ? OR ?PAGET?)
L44            9 SEA FILE=HCAPLUS ABB=ON  L36 AND (PRD<19960228 OR PD<19960228)
L45           52 SEA FILE=HCAPLUS ABB=ON  L20 OR L29 OR L44
L46           42 SEA L45
L47           26 DUP REMOV L46 (16 DUPLICATES REMOVED)

=> d ibib abs l47 1-26

L47  ANSWER 1 OF 26  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
     DUPLICATE 1
ACCESSION NUMBER:    1996:480420  BIOSIS
DOCUMENT NUMBER:     PREV199699195676
TITLE:               Regulation of avian osteoclastic H+-ATPase and bone
                     resorption by tamoxifen and calmodulin
                     antagonists: Effects independent of steroid receptors.
AUTHOR(S):           Williams, John P.; Blair, Harry C.; McKenna, Margaret A.;
                     Jordan, S. Elizabeth; McDonald, Jay M. [Reprint author]
CORPORATE SOURCE:    Dep. Pathol. 509 LHRB, Univ. Alabama at Birmingham,
                     Birmingham, AL 35294-0007, USA
SOURCE:              Journal of Biological Chemistry, (1996) Vol. 271,
                     No. 21, pp. 12488-12495.
                     CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE:       Article
LANGUAGE:            English
ENTRY DATE:          Entered STN: 24 Oct 1996
                     Last Updated on STN: 24 Oct 1996
AB   We used highly purified avian osteoclasts and isolated membranes from
     osteoclasts to study effects of tamoxifen, 4-hydroxytamoxifen, calmodulin
     antagonists, estrogen, diethylstilbestrol, and the anti-estrogen ICI
     182780 on cellular degradation of 3H-labeled bone in vitro and on membrane
     HCl transport.  Bone resorption was reversibly inhibited by tamoxifen,
     4-hydroxytamoxifen, and trifluoperazine with IC-50 values of apprx 1 mu-M.
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Diethylstilbestrol and 17-beta-estradiol had no effects on bone resorption at receptor-saturating concentrations, while ICI 182780 inhibited bone resorption at concentrations greater than 1 mu-M. At these concentrations ICI 182780, like tamoxifen, inhibits calmodulin-stimulated cyclic nucleotide phosphodiesterase activity. Membrane HCl transport. assessed by ATP-dependent acridine orange uptake. wits unaffected by 17-beta-estradiol and diethylstilbestrol it concentrations up to 10 mu-M, while ICI 182780 inhibited HCl transport at concentrations greater than 1 mu-M. In contrast HCl transport was inhibited by tamoxifen, 4-hydroxytamoxifen, and the calmodulin antagonist, trifluoperazine and calmidazolium, with IC-50 values of 0.25-1.5 mu-M. These results suggested the presence of a membrane-associated non-steroid receptor for tamoxifen in osteoclasts. Tamoxifen binding studies demonstrated saturable binding in the osteoclast particulate fraction, but not in the nuclear or cytosolic fractions. Membranes enriched in ruffled border by differential centrifugation following nitrogen cavitation showed binding consistent with one site, K-d apprx 1 mu-M. Our findings indicate that tamoxifen inhibits osteoclastic HCl transport by binding membrane-associated target(s). probably similar or related to calmodulin antagonist targets. Further, effects of estrogens or highly specific anti-estrogens on bone turnover do not support the hypothesis of a direct effect on osteoclasts by these compounds in this species.

L47 ANSWER 2 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 2

ACCESSION NUMBER: 1996:370316 BIOSIS
DOCUMENT NUMBER: PREV199699092672
TITLE: Time-dependent changes in biochemical bone markers and serum cholesterol in ovariectomized rats: Effects of raloxifene HCl, tamoxifen, estrogen, and alendronate.
AUTHOR(S): Frolik, C. A. [Reprint author]; Bryant, H. U.; Black, E. C.; Magee, D. E.; Chandrsekhar, S.
CORPORATE SOURCE: Lilly Corporate Cent., Indianapolis, IN 46285, USA
SOURCE: Bone (New York), (**1996**) Vol. 18, No. 6, pp. 621-627.
CODEN: BONEDL. ISSN: 8756-3282.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 1996
Last Updated on STN: 15 Aug 1996

AB Bone loss associated with postmenopausal osteoporosis can be reduced by treatment with antiresorptive agents such as estrogen or bisphosphonates. Whereas bisphosphonates primarily affect bone loss, estrogens have an advantage of also lowering serum cholesterol levels, although they have a detrimental effect in the uterus. Recently, raloxifene HCl, a selective estrogen receptor modulator (SERM), has been shown to decrease both bone loss and cholesterol levels without the negative uterine effects. These antiresorptive agents reduce bone turnover, which can be evaluated by measuring bone turnover markers. To compare the effects of estrogen, two SERMs (raloxifene HCl and tamoxifen), and alendronate, a bisphosphonate that inhibits bone loss by an estrogen-independent pathway, on metabolic bone markers and cholesterol levels, rats were ovariectomized 2 weeks prior to 3 weeks of daily oral treatment with raloxifene HCl (3 mg/kg), ethynyl estradiol (0.1 mg/kg), tamoxifen (3 mg/kg), or alendronate (3 mg/kg). Raloxifene HCl, tamoxifen, and ethynyl estradiol reduced serum cholesterol to levels below control values within 4 days after initiation of treatment, whereas alendronate had no effect. After 3 weeks of treatment, serum cholesterol values in ethynyl estradiol treated animals, although still below the control value, had risen 6.4-fold; raloxifene HCl and tamoxifen values rose by only 1.4-1.5-fold. Therefore, compared with

estrogen, SERMs may have a longer-term suppressive effect on serum cholesterol. At 4 days of treatment, ovariectomized rats had a 1.4-fold increase in serum osteocalcin level compared with controls. Ethynyl estradiol lowered this level within 1 week of treatment by 18%, with a more pronounced reduction of 34% at 3 weeks. In contrast, raloxifene HCI, tamoxifen, or alendronate had very little effect after the first week (6% to 13% reduction), although there was an 18% to 25% reduction by 3 weeks. Urinary pyridinoline levels, elevated 1.4-fold in the ovariectomized rat compared with controls 2 weeks after surgery, were reduced to control values after 2 weeks of treatment with raloxifene HCl, ethynyl estradiol, tamoxifen, or alendronate. These data support the concept that estrogen, raloxifine HCl, **tamoxifen**, and alendronate inhibit **bone loss** in the ovariectomized animal by reducing bone resorption. The results also indicate that for treatment of postmenopausal **osteoporosis**, **raloxifene** HCl may have an advantage over the other antiresorptives studied in having both nonuterotrophic and hypocholesterolemic effects in addition to its ability to inhibit bone resorption.

L47 ANSWER 3 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 3

ACCESSION NUMBER: 1995:414394 BIOSIS
DOCUMENT NUMBER: PREV199598428694
TITLE: **Droloxifene** prevents ovariectomy-induced **bone loss** in tibiae and femora of aged female rats: A dual-energy x-ray absorptiometric and histomorphometric study.
AUTHOR(S): Chen, Hong Ka [Reprint author]; Ke, Hua Zhu [Reprint author]; Jee, Webster S. S.; Ma, Yan Fei; Pirie, Christine M.; Simmons, Hollis A.; Thompson, David D.
CORPORATE SOURCE: Dep. Cardiovascular Metabolic Dis., Cent. Res. Div., Pfizer Inc., Box 0539, Eastern Point Rd., Groton, CT 06340, USA
SOURCE: Journal of Bone and Mineral Research, (**1995**) Vol. 10, No. 8, pp. 1256-1262.
CODEN: JBMREJ. ISSN: 0884-0431.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Sep 1995
Last Updated on STN: 27 Sep 1995

AB Our previous studies indicated that droloxifene (DRO), a tissue-specific estrogen antagonist/agonist, prevented bone loss without causing uterine hypertrophy in growing ovariectomized (OVX) rats. Using dual-energy X-ray absorptiometry (DXA) and bone histomorphometry, the current study compared the efficacy of DRO to 17-beta-estradiol (E-2) in preventing OVX-induced bone loss in tibiae and femora of 19-month-old rats to determine whether DRO had similar skeletal effects as E-2 in aged female rats. Sprague-Dawley female rats were OVX or sham-operated (sham) at 19 months of age. The sham-operated rats were treated with vehicle (oral), while the OVX rats were treated with vehicle (oral), E-2 at 30 mu-g/kg (sc), or DRO at 2.5, 5, or 10 mg/day (oral) for 8 weeks. Bone mineral density (BMD) of whole femora (WF), distal femoral metaphyses (DFM), femoral shafts (FS), and proximal femora (PF) was determined using DXA. Static and dynamic cancellous bone histomorphometric analyses were performed in double-labeled undecalcified longitudinal sections from proximal tibial metaphyses. Ovariectomy for 8 weeks significantly reduced the BMD of WF, DFM, FS, and PF (from -6 to -15%). Treatment with E-2 completely prevented the decreases in BMD of WF and DIM and had no significant effects in BMD of FS and PF in aged OVX rats. The decrease in BMD of DIM induced by OVX was prevented by treatment with DRO at all dose levels. In addition, DRO at 10 mg/day prevented OVX-induced decreases in BMD of WF,

FS, and PF. Furthermore, proximal tibial cancellous bone histomorphometric results showed that OVX significantly decreased the trabecular bone volume by 34% and increased the activation frequency by 104% while it nonsignificantly increased other indices including percent eroded perimeter, mineral apposition rate, and bone formation rate per bone volume compared with sham-operated controls. Treatment with E-2 or DRO at all dose levels completely prevented the OVX-induced decreases in trabecular bone volume and increases in bone turnover, indicating that DRO is an estrogen agonist in bone in aged OVX rats. Together with the previous findings that DRO inhibited body weight gain, reduced total serum cholesterol, and had no effect on uterine weight, we conclude that DRO is as efficacious as E-2 in preventing OVX-induced bone loss and inhibiting bone turnover but without estrogenic uterine effects in aged OVX rats. These data suggest that DRO may be superior to E-2 for the treatment of postmenopausal and senile osteoporoses.

L47 ANSWER 4 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 4
ACCESSION NUMBER: 1995:210614 BIOSIS
DOCUMENT NUMBER: PREV199598224914
TITLE: Longitudinal and Cross-Sectional Analysis of Raloxifene Effects on Tibiae from Ovariectomized Aged Rats.
AUTHOR(S): Sato, Masahiko [Reprint author]; Kim, John; Short, Lorri L.; Slemenda, Charles W.; Bryant, Henry U.
CORPORATE SOURCE: MC 797, Dep. Endorcine Res., Lilly Corp. Cent., Indianapolis, IN 46285, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (**1995**) Vol. 272, No. 3, pp. 1252-1259.
CODEN: JPETAB. ISSN: 0022-3565.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 1995
Last Updated on STN: 23 May 1995

AB To extend and confirm previous data, we examined the effects of raloxifene on the proximal tibia of ovariectomized rats, aged 6 months, longitudinally and cross-sectionally by computed tomography (pQCT) and then compared the effects to those of orally dosed estrogen. Comparative analysis of phantoms and rat bones showed that the pQCT is precise and correlates with a Hologic QDR 1000W (DXA) with R = 0.999 but is capable of measuring significant differences between groups when the DXA cannot. This may reflect the ability of the pQCT to determine bone volume, mineral content (mg) and volumetric mineral density (mg/cm-3), compared with two-dimensional analyses performed with DXA. Longitudinal analysis of the proximal tibia in vivo showed a significant 17% reduction in mineral density 31 days after ovariectomy. Examination of the images from ovariectomized rats showed a progressive increase in the cross-sectional area of the proximal tibiae, loss of trabecular bone, widening of marrow spaces and thinning of the cortical bone wall opposite the fibula. Regression analysis of the dosedependent protective effects of raloxifene showed the half-maximal efficacy on tibiae mineral density to be ED-50 = 0.4 mg/kg/day per os by pQCT and 0.2 mg/kg/day by DXA. By comparison, 17-alpha ethynyl estradiol showed dose-dependent effects with ED-50 = 0.013 mg/kg/day per os by pQCT. Both raloxifene and ethynyl estradiol had beneficial effects on serum lipids, producing 50% reduction of cholesterol at 0.1 mg/kg/ day raloxifene and 80% reduction with 0.01 mg/kg/day ethynyl estradiol. However, raloxifene up to 10 mg/kg/day had little effect on uterine weight, whereas 0.01 mg/kg/day ethynyl estradiol increased uterine wet weight by 300%. These data show that although ethynyl estradiol is 25 times more potent than **raloxifene** in preventing **bone loss** due to ovariectomy in an aged rat model, raloxifene may have

advantages over hormone replacement in the treatment of bone loss due to estrogen deficiency.

L47 ANSWER 5 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 5
ACCESSION NUMBER: 1997:70099 BIOSIS
DOCUMENT NUMBER: PREV199799369302
TITLE: **Raloxifene** prevents **bone loss** in lumbar spine and femur in aged ovariectomized rats.
AUTHOR(S): Wang, Q. [Reprint author]; Hassager, C.; Wang, S.; Riis, B. Juel; Christiansen, C.
CORPORATE SOURCE: Bone Mineral Research Lab., Henry Ford Hosp., E and R 7092, 2799 West Grand Blvd., Detroit, MI 48202, USA
SOURCE: European Journal of Experimental Musculoskeletal Research, (**1995**) Vol. 4, No. 3-4, pp. 171-175.
ISSN: 0803-5288.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Feb 1997
Last Updated on STN: 11 Feb 1997

AB Raloxifene has recently been shown to prevent osteopenia in oophorectomized (OVX) young rats. We have investigated the effect of raloxifene on bone mineral content (BMC) and density (BMD) in more mature rats. One-year-old female Sprague-Dawley rats were divided into five groups: SHAM: Sham operated, placebo treated; OVX: OVX, placebo treated; L-Ral: OVX, 0.1 mg/kg/day per os of raloxifene; H-Ral: OVX, 1.0 mg/kg/day per os of raloxifene and; E2: OVX, 0.5 mg/kg/dag per os of 17-beta-estradiol. The rats were killed after 12 weeks. The BMC and BMD of the excised left femur and lumbar spine were measured by dual energy X-ray absorptiometry (DXA, Hologic QDR-2000) in vitro. The body weight remained unchanged in the E-2 and H-Ral groups, decreased slightly (40/o) in the L-Ral group and increased slightly increase in lean tissue mass (measured by DXA). After 12 weeks the OVX group had 6-8% lower BMD at the femur and (4-5%) in the SHAM and OVX groups. The increase in body weight in the SHAM and OVX groups was caused by an lumbar spine. The OVX induced osteopenia was prevented by E-2 and both doses of raloxifene in the lumbar spine, but only significantly by E-2 and low dose raloxifene in the femur. The differences in BMD between the groups were caused by differences in BMC and not by differences in area. We conclude that 0.1 mg/kg/day of raloxifene given orally prevents OVX induced osteopenia in the aged (1-year-old) rat.

L47 ANSWER 6 OF 26 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 95136136 EMBASE
DOCUMENT NUMBER: 1995136136
TITLE: [Tamoxifen and bone metabolism: Comment].
TAMOXIFEN UND **OSTEOPOROSE**: KOMMENTAR.
AUTHOR: Dunst J.
CORPORATE SOURCE: Germany
SOURCE: Strahlentherapie und Onkologie, (**1995**) Vol. 171, No. 2, pp. 113-114.
ISSN: 0179-7158 CODEN: STONE4
COUNTRY: Germany
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 006 Internal Medicine
009 Surgery
014 Radiology
016 Cancer
031 Arthritis and Rheumatism

037 Drug Literature Index
LANGUAGE: German
ENTRY DATE: Entered STN: 950523
Last Updated on STN: 950523
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L47 ANSWER 7 OF 26 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 95071658 EMBASE
DOCUMENT NUMBER: 1995071658
TITLE: Prostaglandin E2 administration prevents bone loss induced by orchidectomy in rats.
AUTHOR: Li M.; Jee W.S.S.; Ke H.Z.; Tang L.Y.; Ma Y.F.; Liang X.G.; Setterberg R.B.
CORPORATE SOURCE: Division of Radiobiology, Building 586, Utah University School of Medicine,Salt Lake City, UT 84112, United States
SOURCE: Journal of Bone and Mineral Research, (**1995**) Vol. 10, No. 1, pp. 66-73.
ISSN: 0884-0431 CODEN: JBMREJ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003. Endocrinology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 950329
Last Updated on STN: 950329

AB The objects of this study were to investigate whether prostaglandin E2 (PGE2) can prevent orchidectomy (ORX)-induced cancellous bone loss in growing male rats, and to determine the differential effects of PGE2 on sham-operated (sham) and ORX male rats. Fourteen-week-old Sprague-Dawley male rats were divided into groups of basal, vehicle-treated sham, PGE2-treated sham, vehicle-treated ORX, and PGE2-treated ORX rats for either 3 or 9 weeks. PGE2 was given at 6 mg/kg body weight daily by subcutaneous injection. Static and dynamic cancellous bone histomorphometry were performed on double-fluorescent labeled undecalcified proximal tibial metaphyseal sections. No effect was observed by ORX on body weight or longitudinal bone growth rate when compared with sham-operated controls. However, androgen deficiency caused significant increases in percent eroded perimeter, mineral apposition rate, and bone turnover (bone-volume-referent-bone formation rate), which resulted in a significant decrease in trabecular bone number, increase in trabecular separation, and a nonsignificant decrease in trabecular bone area by 3 weeks of ORX. After 9 weeks of ORX, trabecular bone area and number were significantly decreased, and trabecular separation, percent eroded perimeter, and the index of bone turnover (bone-volume-referent-bone formation rate) remained significantly increased while the index of bone formation (tissue-volume-referent-bone formation rate) was nonsignificantly decreased when compared with sham controls. When 6 mg PGE2/kg/day was given for 3 and 9 weeks, similar anabolic effects were observed in sham and ORX rats. PGE2 caused significant decreases in body weight and longitudinal bone growth rate and significant increases in trabecular bone area, thickness, labeling perimeter, mineral apposition rate, and tissue-volume-referent-bone formation rate in both sham and ORX rats when compared with their respective controls. In sham-operated rats, PGE2 had no effect on percent eroded perimeter after 3 weeks of treatment, whereas after 9 weeks PGE2 caused a significant increase in this index. PGE2 partially inhibited the increase in percent eroded perimeter induced by ORX at week 3, but had no effect on this parameter at week 9 as compared with ORX controls. In summary, the new findings from current

study indicated that **PGE2** can prevent **bone loss** induced by ORX and the anabolic skeletal effect of PGE2 independent of the presence of androgen and longitudinal growth and occurs mainly on the pre-existing bone surface.

L47 ANSWER 8 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 6

ACCESSION NUMBER: 1994:350185 BIOSIS
DOCUMENT NUMBER: PREV199497363185
TITLE: Dual-energy X-ray absorptiometry of raloxifene effects on the lumbar vertebrae and femora of ovariectomized rats.
AUTHOR(S): Sato, Masahiko [Reprint author]; McClintock, Cindy; Kim, John; Turner, Charles H.; Bryant, Henry U.; Magee, David; Slemenda, Charles W.
CORPORATE SOURCE: MC 620, Dep. Endocrine Res., Lilly Corp. Cent., Indianapolis, IN 46285, USA
SOURCE: Journal of Bone and Mineral Research, (**1994**) Vol. 9, No. 5, pp. 715-724.
CODEN: JBMREJ. ISSN: 0884-0431.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Aug 1994
Last Updated on STN: 18 Nov 1994

AB A new potential therapeutic agent for postmenopausal **osteoporosis**, **raloxifene**, previously known as keoxifene, was evaluated by x-ray densitometry and more traditional techniques in quantitating the short-term (4-5 weeks) effects of ovariectomy on bones from 6-month-old rats. A Hologic QDR 1000/W and, to a limited extent, a Lunar DPXL, was used to quantitate ovariectomy, estrogen replacement, and raloxifene effects on vertebrae, femora, and tibiae. Both instruments performed well with precisions of 1.6% (Hologic) and 0.9% (Lunar) for anesthetized rats, which improved to 0.4% (Hologic) and 0.5% (Lunar) when the same rats were frozen. The lumbar vertebrae L1-4 showed a 12% decrease in bone mineral density 4 weeks after ovariectomy, compared with a 9% decrease for femora. Tibiae were also examined, but edge-detection problems prevented reproducible analysis of this site in vivo. The decrease in bone mineral density postovariectomy, especially for femora, was found to include both an increase in the projected area and a slight but not significant decrease in the bone mineral content of L1-4 and femora. These changes in density parameters of femora were supported by a decrease in dry weight and volume and a marginal increase in the second moment of inertia I for the identical femora examined ex vivo. Examination of individual lumbar vertebrae L1-5 suggested that the bone mineral density of L3 changes most dramatically in response to ovariectomy, but present techniques lack the spatial resolution and precision to quantitate bone changes reliably in individual vertebrae. 17-beta-Estradiol administered at 100 mu-g/kg/day subcutaneously inhibited ovariectomy effects on L1-4 bone mineral density, femoral moment of inertia, dry weight, and volume and to a lesser extent, femoral bone mineral density. A nonsteroidal compound, raloxifene HCl, at 1 mg/kg/day per os, had bone effects and effects on body weight that were largely indistinguishable from those of 17-beta-estradiol; however, raloxifene did not produce the uterotrophic effects observed with estrogen. The half-maximal efficacious dose of raloxifene on L1-4 bone mineral density was between 0.1 and 1.0 mg/kg/day per os. These data show that dual-energy x-ray absorptiometry compares favorably with traditional methods in quantitating bone changes caused by ovariectomy in small rodents, that L1-4 is a more sensitive region than whole femora in evaluating the effect of estrogen deficiency on **bone loss**, and the **raloxifene** may have promise as a treatment for conditions characterized by excessive bone loss after ovariectomy.

L47 ANSWER 9 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:15199 BIOSIS
DOCUMENT NUMBER: PREV199598029499
TITLE: **Tamoxifen** protects against accelerated **bone loss** from artificial castration with goserelin in the adjuvant setting.
AUTHOR(S): Fornander, T. [Reprint author]; Wilking, N.; Rutqvist, Lars-Erik; Von Schoultz, Eva
CORPORATE SOURCE: Dep. General Oncol., Stockholm Soder Hosp., S-118 83 Stockholm, Sweden
SOURCE: Breast Cancer Research and Treatment, (**1994**) Vol. 32, No. SUPPL., pp. 67.
Meeting Info.: 17th Annual San Antonio Breast Cancer Symposium on Breast Cancer Research and Treatment. San Antonio, Texas, USA. December 6-10, 1994.
CODEN: BCTRD6. ISSN: 0167-6806.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jan 1995
Last Updated on STN: 5 Jan 1995

L47 ANSWER 10 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 7
ACCESSION NUMBER: 1994:132119 BIOSIS
DOCUMENT NUMBER: PREV199497145119
TITLE: **Raloxifene** (LY139481 HCl) prevents **bone loss** and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats.
AUTHOR(S): Black, Larry J.; Sato, Masahiko; Rowley, Ellen R.; Magee, David E.; Bekete, Aster; Williams, Daniel C.; Cullinan, George J.; Bendele, Raymond; Kaufmann, Raymond F.; Bensch, William R.; Frolik, Charles A.; Termine, John D.; Bryant, Henry U. [Reprint author]
CORPORATE SOURCE: Skeletal Diseases Res., Lilly Corp. Cent., Eli Lilly Co., Indianapolis, IN 56285, USA
SOURCE: Journal of Clinical Investigation, (**1994**) Vol. 93, No. 1, pp. 63-69.
CODEN: JCINAO. ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 1994
Last Updated on STN: 18 Nov 1994

AB There is a medical need for an agent with the positive effects of estrogen on bone and the cardiovascular system, but without the negative effects on reproductive tissue. Raloxifene (LY139481 HCl) is a benzothiophene derivative that binds to the estrogen receptor and inhibits the effects of estrogen on the uterus. In an ovariectomized (OVX) rat model we investigated the effects of **raloxifene** on **bone loss** (induced by estrogen deficiency), serum lipids, and uterine tissue. After oral administration of raloxifene for 5 wk (0.1-10 mg/kg per d) to OVX rats, bone mineral density in the distal femur and proximal tibia was significantly greater than that observed in OVX controls (ED-50 of 0.03-0.3 mg/kg). Serum cholesterol was lower in the raloxifene-treated animals, which had a minimal effective dose of 0.1 mg/kg and an approximate oral ED-50 of 0.2 mg/kg. The effects of raloxifene on bone and serum cholesterol were comparable to those of a 0.1-mg/kg per d oral dose of ethynyl estradiol. Raloxifene diverged dramatically from estrogen in its lack of significant estrogenic effects on uterine tissue. Ethynyl

estradiol produced a marked elevation in a number of uterine histologic parameters (e.g., epithelial cell height, stromal eosinophilia). These data suggest that raloxifene has promise as an agent with beneficial bone and cardiovascular effects in the absence of significant uterine effects.

L47 ANSWER 11 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 8

ACCESSION NUMBER: 1993:526746 BIOSIS
DOCUMENT NUMBER: PREV199396140153
TITLE: Tamoxifen reduces bone turnover and prevents lumbar spine and proximal femoral bone loss in early postmenopausal women.
AUTHOR(S): Ward, R. L.; Morgan, G.; Dalley, D.; Kelly, P. J.
CORPORATE SOURCE: Garvan Inst. Med. Res., Victoria St, Sydney, NSW 2010, Australia
SOURCE: Bone and Mineral, (**1993**) Vol. 22, No. 2, pp. 87-94.
CODEN: BOMIET. ISSN: 0169-6009.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 1993
Last Updated on STN: 20 Nov 1993

AB Although widely used for its anti-estrogen properties tamoxifen has estrogen like effects of a number of tissues including bone and liver. Previous studies suggest a preservation of lumbar spine density in postmenopausal women but the effect on the hip had not been addressed. To determine whether **tamoxifen** prevents **bone loss** in the early postmenopausal period bone mineral density at the lumbar spine and femoral neck was measured using dual energy X-ray absorptiometry at presentation and 6 monthly thereafter for 1 year in a prospective controlled study. Also indices of bone turnover, serum osteocalcin and urinary hydroxyproline excretion, were assessed. Fifteen early postmenopausal women with Stage I or II breast cancer treated with tamoxifen and 21 normal postmenopausal women were studied. Sex hormone binding globulin and antithrombin III levels in serum were also measured as indices of the hepatic estrogenic activity. Tamoxifen (20 mg daily) prevented bone loss at the femoral neck and lumbar spine. Median rates of change in bone mineral density (%/year) for the tamoxifen group were +0.09%/year in the lumbar spine and 1.4%/year in the femoral neck compared with -2.3%/year and -1.8%/year for the control group (P=0.04 and 0.03, respectively). Tamoxifen resulted in a significant decrease in both serum osteocalcin and urinary hydroxyproline by 6 months of treatment and this effect persisted for the 12 months of observation. An increase in sex hormone binding globulin and a decline in antithrombin III levels was also observed. These data indicate that, in recently, postmenopausal women **tamoxifen** prevented **bone loss** at both the lumbar spine and femur and reduced bone turnover.

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ACCESSION NUMBER: 92120047 EMBASE
DOCUMENT NUMBER: 1992120047
TITLE: Tamoxifen protects against steroid-induced bone loss.
AUTHOR: Fentiman I.S.; Saad Z.; Caleffi M.; Chaudary M.A.; Fogelman I.
CORPORATE SOURCE: ICRF Clinical Oncology Unit, Guy's Hospital,London SE1 9RT, United Kingdom
SOURCE: European Journal of Cancer, (**1992**) Vol. 28, No. 2-3, pp. 684-685.
ISSN: 0964-1947 CODEN: EJCAEL

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 920515
Last Updated on STN: 920515

AB As part of a clinical trial of adjuvant endocrine treatment in postmenopausal women with operable breast cancer serial bone density measurements have been performed by dual photon absorptiometry. Tamoxifen alone was given to 26 women, and 20 received additional prednisolone. By 24 months after entry there was no significant difference between mean bone density of the two groups, nor any significant change from baseline levels. There was a mean gain of 0.46% in the tamoxifen group and 1.95% in those given additional prednisolone. Thus the predicted steroid-induced **bone loss** was inhibited by **tamoxifen**. This may be of more general use in prevention of osteoporosis in patients requiring long-term steroid treatment.

L47 ANSWER 13 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 9
ACCESSION NUMBER: 1992:349998 BIOSIS
DOCUMENT NUMBER: PREV199294042223; BA94:42223
TITLE: NEW EVIDENCE THAT **TAMOXIFEN** DOES NOT INDUCE **OSTEOPOROSIS** A NUCLEAR ACTIVATION ANALYSIS AND ABSORPTIOMETRY STUDY.
AUTHOR(S): KALEF-EZRA J [Reprint author]; GLAROS D; KLOUVAS G; HATZIKONSTANTINOU J; KARANTANAS A; SIAMOPOULOS K C; PAVLIDIS N
CORPORATE SOURCE: MED PHYSICS DEP, MED SCH, UNIV IOANNINA 451 10 IOANNINA, GREECE
SOURCE: British Journal of Radiology, (**1992**) Vol. 65, No. 773, pp. 417-420.
CODEN: BJRAAP. ISSN: 0007-1285.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 29 Jul 1992
Last Updated on STN: 30 Jul 1992

AB The possibility of increased risk for osteoporosis in breast cancer patients treated with tamoxifen was investigated. 26 patients aged 41-65 years without skeletal metastases were studied. All patients were treated with 20 mg/d tamoxifen for a mean time of 22 months, The data obtained by in vivo neutron activation analysis of the phosphorus content in hands, were supplemented with data obtained by single photon absorptiometry in the forearm and radiographic morphometry. Comparison of the data with that of age and sex matched normal controls showed that breast cancer patients treated with tamoxifen are not prone to osteoporosis.

L47 ANSWER 14 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 10
ACCESSION NUMBER: 1992:261432 BIOSIS
DOCUMENT NUMBER: PREV199293137757; BA93:137757
TITLE: PROSTAGLANDIN E-2 PREVENTS DISUSE-INDUCED CORTICAL BONE LOSS.
AUTHOR(S): JEE W S S [Reprint author]; AKAMINE T; KE H Z; LI X J; TANG L Y; ZENG Q Q

CORPORATE SOURCE: BUILDING 586, DIV RADIOBIOLOGY, UNIV UTAH, SALT LAKE CITY, UTAH 84112, USA
SOURCE: Bone (New York), (**1992**) Vol. 13, No. 2, pp. 153-159.
CODEN: BONEDL. ISSN: 8756-3282.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 23 May 1992
Last Updated on STN: 23 May 1992

AB The object of this study was to determine whether prostaglandin E2 (PGE2) can prevent disuse (underloaded)-induced cortical bone loss as well as add extra bone to underloaded bones. Thirteen-month-old retired female Sprague-Dawley breeders served as controls or were subjected to simultaneous right hindlimb immobilization by bandaging and daily subcutaneous dose of 0, 1,3, or 6 mg PGE2/kg/d for two and six weeks. Histomorphometric analyses were performed on double-fluorescent labeled undecalcified tibial shaft sections (proximal to the tibiofibular junction). Disuse-induced cortical bone loss occurred by enlarging the marrow cavity and increasing intracortical porosity. PGE2 treatment of disuse shafts further increased intracortical porosity above that in disuse alone controls. This bone loss was counteracted by enhancement of periosteal and corticoendosteal bone formation. Stimulation of periosteal and corticoendosteal bone formation slightly enlarged the total tissue (cross-sectional) area and inhibited marrow cavity enlargement. These PGE2-induced activities netted the same percentage of cortical bone with a different distribution than the beginning and age-related controls. These findings indicate the PGE2-induced increase in bone formation compensated of the disuse and **PGE2**-induced **bone loss**, and thus prevented immobilization-induced bone loss.

L47 ANSWER 15 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 11
ACCESSION NUMBER: 1992:473020 BIOSIS
DOCUMENT NUMBER: PREV199294104395; BA94:104395
TITLE: TAMOXIFEN IN THE RAT PREVENTS ESTROGEN-DEFICIENCY BONE LOSS ELICITED WITH THE LHRH AGONIST BUSERELIN.
AUTHOR(S): GOULDING A [Reprint author]; GOLD E; FENG W
CORPORATE SOURCE: DEP MEDICINE, UNIVERSITY OTAGO MEDICAL SCHOOL, PO BOX 913, DUNEDIN, NEW ZEALAND
SOURCE: Bone and Mineral, (**1992**) Vol. 18, No. 2, pp. 143-152.
CODEN: BOMIET. ISSN: 0169-6009.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Oct 1992
Last Updated on STN: 28 Oct 1992

AB In young women chronic use of luteinizing hormone releasing hormone (LHRH) agonists such as buserelin to treat endometriosis leads to estrogen-deficiency bone loss. Tamoxifen citrate is an estrogen agonist/antagonist which protects the skeleton from osteopenia when ovarian hormones are depleted. The present study ws undertaken to determine whether tamoxifen citrate (20 mg/kg body wt/week s.c.) could prevent the osteopenic effect of buserelin (25 μg/kg body wt/day s.c.). Four groups of rats with 45Ca-labelled bones were studied for 4 weeks: group A - placebo controls; group B - buserelin; Group C-tamoxifen; group D - buserelin + tamoxifen. Bone resorption was monitored by measuring the urinary excretion of 45Ca and hydroxyproline. Interestingly buserelin lowered both blood 17β-estradiol values and uterine weights in the

presence and absence of tamoxifen. However, tamoxifen slowed bone breakdown and inhibited the bone-thinning effects of buserelin. Total body calcium values (mg; means ± S.D.) were: 2227 ± 137; 1926 ± 124; 2233 ± 94 and 2268 ± 163, in groups A to D respectively. Osteopenia was thus present only in group B ($P < 0.001$). Because **tamoxifen** inhibits estrogen-deficiency **bone loss** in buserelin-treated rats without depressing the hypoestrogenic actions of this LHRH-agonist, we suggest that use of tamoxifen to protect the skeleton during LHRH-agonist therapy in young women should be explored. Tamoxifen citrate might also help to prevent postmenopausal osteoporosis.

L47 ANSWER 16 OF 26 EMBASE

ACCESSION NUMBER: 92300002 EMBASE
DOCUMENT NUMBER: 1992300002
TITLE: Prostaglandin E2 prevents ovariectomy-induced cancellous bone loss in rats.
AUTHOR: Ke H.Z.; Li M.; Jee W.S.S.
CORPORATE SOURCE: Division of Radiobiology, University of Utah,Salt Lake City, UT 84112, United States
SOURCE: Bone and Mineral, (**1992**) Vol. 19, No. 1, pp. 45-62.
ISSN: 0169-6009 CODEN: BOMIET
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 033 Orthopedic Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 921025
Last Updated on STN: 921025

AB The object of this study was to determine whether prostaglandin E2 (PGE2) can prevent ovariectomy-induced cancellous bone loss. Thirty-five 3-month-old female Sprague-Dawley rats were divided into two groups. The rats in the first group were ovariectomized (OVX) while the others received sham operation (sham-OVX). The OVX group was further divided into three treatment groups. The daily doses for the three groups were 0, 1 and 6 mg PGE2/kg for 90 days. Bone histomorphometric analyses were performed on double-fluorescent-labeled undecalcified proximal tibial metaphysis (PTM). We confirmed that OVX induces massive cancellous bone loss (-80%) and a higher bone turnover (+143%). The new findings from the present study demonstrate that bone loss due to ovarian hormone deficiency can be prevented by a low-dose (1 mg) daily administration of PGE2. Furthermore, a higher-dose (6 mg) daily administration of PGE2 not only prevents bone loss but also adds extra bone to the proximal tibial metaphyses. PGE2 at the 1-mg dose level significantly increased trabecular bone area, trabecular width, trabecular node density, density of node to node, ratio of node to free end, and thus significantly decreased trabecular separation from OVX controls. At this dose level, these same parameters did not differ significantly from sham-OVX controls. However, at the 6-mg dose level PGE2, there were significant increases in trabecular bone area, trabecular width, trabecular node density, density of node to node, and ratio of node to free end, while there was significant decrease in trabecular separation from both OVX and sham-operated controls. The changes in indices of trabecular bone microanatomical structure indicated that **PGE2** prevented **bone loss** as well as the disconnection of existing trabeculae. In summary, PGE2 administration to OVX rats decreased bone turnover and increased bone formation parameters resulting in a positive

bone balance that prevented bone loss (in both lower and higher doses) and added extra bone to metaphyses of OVX rats (in higher dose). These findings support the strategy of the use of bone stimulation agents in the prevention of estrogen depletion bone loss (postmenopausal osteoporosis).

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ACCESSION NUMBER: 92271635 EMBASE
DOCUMENT NUMBER: 1992271635
TITLE: [Tamoxifen as a cytostatic agent and for the prevention of osteoporosis: Comment].
TAMOXIFEN ZUR ZYTOSTASE UND **OSTEOPOROSEPROPHYLAXE**: KOMMENTAR.
AUTHOR: Sauer H.
CORPORATE SOURCE: Germany
SOURCE: Fortschritte der Medizin, (**1992**) Vol. 110, No. 21, pp. 11.
ISSN: 0015-8178 CODEN: FMDZAR
COUNTRY: Germany
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
020 Gerontology and Geriatrics
033 Orthopedic Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: German
ENTRY DATE: Entered STN: 921004
Last Updated on STN: 921004
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L47 ANSWER 18 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 12

ACCESSION NUMBER: 1992:284209 BIOSIS
DOCUMENT NUMBER: PREV199294008859; BA94:8859
TITLE: **TAMOXIFEN** PREVENTS **BONE LOSS** IN OVARIECTOMIZED MICE.
AUTHOR(S): BROULIK P D [Reprint author]
CORPORATE SOURCE: 3RD CLINIC INTERNAL MED, FAC MED, CHARLES UNIV, 128 21 PRAHA, CZECH
SOURCE: Endocrine Regulations, (**1991**) Vol. 25, No. 4, pp. 217-219.
ISSN: 1210-0668.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 10 Jun 1992
Last Updated on STN: 10 Jun 1992

AB Bone density and mineral content of the femora were significantly decreased in ovariectomized mice compared with intact control animals. Tamoxifen treated ovariectomized mice did not develop any decrease either in the bone density or in calcium and phosphate content of the femora which were observed in ovariectomized mice. In addition, the weight of uterus in tamoxifen treated ovariectomized mice was the same as in intact controls. It was concluded that tamoxifen administered in vivo prevented the loss of bone mineral and uterus weight in ovariectomized mice and thus it showed a true estrogen like action in this respect.

L47 ANSWER 19 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1991:95474 BIOSIS
DOCUMENT NUMBER: PREV199191054364; BA91:54364
TITLE: COMBINED USE OF TAMOXIFEN AND DL-15 METHYLPROSTAGLANDIN F-2-ALPHA FOR TERMINATION OF EARLY PREGNANCY.
AUTHOR(S): CHENG L [Reprint author]; ZHOU Y; CHU Y; JIN Z; WANG K; LI Q
CORPORATE SOURCE: DEP OBSTET AND GYNECOL, ZHONG SHAN HOSP, SCH PHARM, SHANGHAI MED UNIV, SHANGHAI
SOURCE: Journal of Shanghai Medical University, (**1990**) Vol. 17, No. 5, pp. 378-381.
CODEN: SYDXEE. ISSN: 0257-8131.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: CHINESE
ENTRY DATE: Entered STN: 11 Feb 1991
Last Updated on STN: 12 Feb 1991

AB **Tamoxifen** (Tam) combined with dl-15-methyl prostaglandin F2α (15-m- **PGF2α**) were used in 34 healthy women in early pregnancy requesting abortion. In 8 of them radioimmunoassay of serum hormones were done before and after Tam administration. In another group of 18 early pregnant women applying for abortion, Tam was given to 9 of them to study its effects on decidual tissues, the remaining 9 cases had vacuum aspiration and served as controls. In 34 cases treated by Tam and dl-15-m-PGF2α, 31 (91.18%) resulted in complete abortion, 1 (2.94%) incomplete abortion and 2 (5.88%) failed. The β-hCG doubling time was delayed markedly to 7.85 ± 2.25 days (.ovrhdot.x ± SE) after Tam administration, suggesting that Tam has inhibitory action on the secretion of β-hCG in early pregnancy. Decidual cytoplasmic estradiol (E2), progesterone and nuclear E2 receptor levels showed statistically insignificant decrease, after Tam administration ($P > 0.05$).

L47 ANSWER 20 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 13
ACCESSION NUMBER: 1990:221374 BIOSIS
DOCUMENT NUMBER: PREV199089118664; BA89:118664
TITLE: EFFECTS OF CLOMIPHENE AND TAMOXIFEN IN-VIVO ON THE BONE-RESORBING EFFECTS OF PARATHYROID HORMONE AND OF HIGH ORAL DOSES OF CALCITRIOL 1 25 DIHYDROXYVITAMIN D-3 IN RATS WITH INTACT OVARIAN FUNCTION CONSUMING LOW CALCIUM DIET.
AUTHOR(S): GOULDING A [Reprint author]; GOLD E; FISHER L
CORPORATE SOURCE: MED DEP, UNIV OTAGO MED SCH, PO BOX 913, DUNEDIN, NEW ZEALAND
SOURCE: Bone and Mineral, (**1990**) Vol. 8, No. 3, pp. 185-194.
CODEN: BOMIET. ISSN: 0169-6009.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 10 May 1990
Last Updated on STN: 10 May 1990

AB Two experiments were undertaken to study the abilities of clomiphene citrate (20 mg/kg body wt/wk s.c.) and tamoxifen citrate (20 mg/kg body wt/wk s.c.) to slow bone resorption mediated by (a) endogenous parathyroid hormone (PTH) and (b) exogenous calcitriol (1,25(OH)2D3) in vivo in rats with intact ovarian function. Groups of rats with 45Ca-labelled bones were fed a low-calcium (0.01% Ca) diet to stimulate secretion of PTH. Neither clomiphene nor tamoxifen slowed the mobilization of 45Ca from femoral bone or prevented the reduction in bone calcium induced by feeding this diet. Moreover these drugs did not depress the urinary excretion of

45Ca or hydroxyproline. These observations indicated that clomiphene and tamoxifen did not inhibit PTH-mediated bone resorption. Administering calcitriol (50 ng/day) orally for 14 days raised plasma calcium, increased urinary 45Ca and its specific activity and decreased femur 45Ca: all these responses were similar in animls receiving calcitriol alne and calcitriol with clomiphene or tamoxifen. The femur 45Ca values (dpm + 10-3) were: (means ± SD, n = 8) placebo, 1901 ± 127; 1,25(OH)2D3, 1727 ± 96**; clomiphene + 1,25)(OH)2D3, 1694 ± 93**, tamoxifen + 1,25(OH)2D3, 1664 ± 61**. (** = P < 0.01). Thus neither clomiphene nor **tamoxifen** prevented calcitriol-mediated **bone resorption** in vivo in the rat.

L47 ANSWER 21 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 14

ACCESSION NUMBER: 1990:306071 BIOSIS
DOCUMENT NUMBER: PREV199090025038; BA90:25038
TITLE: ELECTRON MICROSCOPIC OBSERVATIONS OF OSTEOBLASTS AND OSTEOCLASTS ON THE MEDULLARY BONE OF TAMOXIFEN-TREATED HENS.
AUTHOR(S): OHASHI T [Reprint author]; KUSUHARA S; ISHIDA K
CORPORATE SOURCE: GRADUATE SCHOOL SCIENCE TECHNOLOGY, NIIGATA UNIVERSITY, NIIGATA 950-21, JPN
SOURCE: Japanese Poultry Science, (**1990**) Vol. 27, No. 2, pp. 122-127.
CODEN: NKKGAB. ISSN: 0029-0254.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 10 Jul 1990
Last Updated on STN: 10 Jul 1990

AB Osteoblasts and osteoclasts on the medullary bone surface in the femurs of laying hens treated with tamoxifen (an antiestrogen) were examined with an electron microscope while an egg was in the magnum or in the shell gland of the oviduct. Most osteoblasts on the medullary bone surface of non-treated hens having an egg in the magnum were characterized by well developed cytoplasm containing a large endoplasmic reticulum and Golgi complexes. And osteoclasts which were distributed very sparsely on the bone surface did not possess ruffled borders. After tamoxifen treatment, however, many osteoblasts had poorly developed cell organelles, but osteoclasts had well developed cytoplasm and extended ruffled borders adjacent to the bone surface. When an egg was in the shell gland, many osteoblasts in both tamoxifen-treated and non-treated hens showed poorly developed cytoplasm, but the osteoclasts had well developed cytoplasm and ruffled borders. These results indicate that osteoblastic bone formation is suppressed and osteoclastic **bone resorption** is accelerated by **tamoxifen** treatment while an egg is in the magnum, and that effects of tamoxifen may not be detected in osteoblasts and osteoclasts while an egg is in the shell gland. Therefore, it is suggested that estrogen stimulates the bone formative functions of osteoblasts and prevents the bone resorptive functions of osteoclasts during the egg laying cycles.

L47 ANSWER 22 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1989:425581 BIOSIS
DOCUMENT NUMBER: PREV198988083839; BA88:83839
TITLE: ESTRADIOL EFFECTS ON PROLIFERATION MESSENGER RNA FOR COLLAGEN AND INSULIN-LIKE GROWTH FACTOR-I AND PARATHYROID HORMONE-STIMULATED ADENYLATE CYCLASE ACTIVITY IN OSTEOBLASTIC CELLS FROM CALVARIAE AND LONG BONES.

AUTHOR(S): ERNST M [Reprint author]; HEATH J K; ROAN G A
CORPORATE SOURCE: DEP BONE BIOL OSTEOPOROSIS RES, MERCK SHARP AND DOHME RES LAB, WEST POINT, PA 19486, USA
SOURCE: Endocrinology, (**1989**) Vol. 125, No. 2, pp. 825-833.
CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 19 Sep 1989
Last Updated on STN: 23 Sep 1989

AB Estradiol (E2) replacement therapy effectively prevents or delays postmenopausal bone loss, but the mode of E2 action on bone is still unknown. Recently, the presence of E2 receptors was described for bone-derived cells. In this study we examined the estrogen responsiveness of osteoblastic cells using the experimentally immortalized calvarial cell lines RCT-1 and RCT-3 as well as primary cultures of calvarial and trabecular bone cells. E2 treatment reduced PTH-stimulated adenylate cyclase activity by 20-30% in RCT cells; th maximum effect was observed after treatment with 1 nM E2 for 4 h or longer. In trabecular cells E2 decreased PTH-stimulated adenylate cyclase activity by 60-80%. After a lag period of at least 48 h, E2 treatment (0.01-10 nM) increased cell number and [3H]thymidine incorporation in both RCT-3 cells and primary cultures of trabecular cells to 20-60% above control values. Half-maximal effects were observed at about 1 nM E2. Antibodies against insulin-like growth factor-I (IGF-I) inhibited thr E2-induced proliferation in a dose-dependent manner without affecting basal growth. Furthermore, E2 treatment increased the steady state levels of IGF-I mRNA 2- to 2.5-fold in calvarial and RTC-3 cells compared to control levels. In addition, E2 (10 nM) increased the level of collagen mRNA more than 2-fold and opposed the suppression of collagen mRNA produced by PTH treatment. The E2 effects were specific to 17β-E2, since they were not observed with the biologically less active stereoisomer 17α-E2 and were blocked by the E2 antagonist tamoxifen (1 μM). Thus, for osteoblastic cells in culture, E2 can directly stimulate proliferation as well as collagen and IGF-I mRNA while decreasing PTH responsiveness; these effects could explain the anabolic and anticatabolic effects of E2 on bone.

L47 ANSWER 23 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1986:160966 BIOSIS
DOCUMENT NUMBER: PREV198681071382; BA81:71382
TITLE: IN-VITRO INHIBITION WITH ANTIESTROGENS OF ESTRADIOL EFFECTS ON PROSTAGLANDIN F-2-ALPHA PRODUCTION BY HUMAN ENDOMETRIUM AND ENDOMETRIAL EPITHELIAL CELLS.
AUTHOR(S): SCHATZ F [Reprint author]; MARKIEWICZ L; BARG P; GURPIDE E
CORPORATE SOURCE: DEP OBSTET GYNECOL REPROD SCI, MOUNT SINAI SCH MED, ONE GUSTAVE L LEVY PLACE, NEW YORK, NY 10029, USA
SOURCE: Endocrinology, (**1986**) Vol. 118, No. 1, pp. 408-412.
CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 26 Apr 1986
Last Updated on STN: 26 Apr 1986

AB It has been previously reported that neither an antiestrogen, actinomycin D, nor cycloheximide inhibited estradiol (E2)-stimulated elevations in uterine prostaglandin F2α (PGF2α) production in ovariectomized rats, suggesting that in contrast to other steroid-initiated events, this

effect on PGF2α may not involve receptor-mediated transcription-dependent actions of E2. To eliminate indirect influences, the ability of antiestrogens to affect PGF2α output was reevaluated during incubations of human secretory endometrium and in cultures of epithelial cells derived from glands isolated from proliferative and secretory tissues. In these preparations, which respond to E2 with marked elevations in **PGF2α** output, **tamoxifen** and its metabolite trans-4-**monohydroxytamoxifen** acted as virtually pure antagonists, counteracting the E2 effect while failing to influence basal **PGF2α** output. Consistent with its effects on other estrogen-mediated end points, trans-4-monohydroxytamoxifen was at least 10 times more potent than **tamoxifen**, eliminating, at a 10-6 M concentration, almost completely the stimulatory effect of 10-8 M E2 on **PGF2**. **alpha**. production by both endometrial fragments and monolayers of epithelial cells.

L47 ANSWER 24 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 15

ACCESSION NUMBER: 1986:164818 BIOSIS
DOCUMENT NUMBER: PREV198681075234; BA81:75234
TITLE: EFFECTS OF THE ANTIESTROGENS **TAMOXIFEN** AND CLOMIPHENE ON **BONE RESORPTION** IN-VITRO.
AUTHOR(S): STEWARD P J [Reprint author]; STERN P H
CORPORATE SOURCE: DEP PHARMACOL, NORTHWEST UNIV, 303 EAST CHICAGO AVE, CHICAGO, ILL 60611, USA
SOURCE: Endocrinology, (**1986**) Vol. 118, No. 1, pp. 125-131.
CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 26 Apr 1986
Last Updated on STN: 26 Apr 1986

AB The in vitro effect of the nonsteroidal antiestrogens tamoxifen (TAM) and clomiphene (CLO) on bone resorption was investigated. TAM (100 μM) and CLO (100 μM) completely blocked PTH (2 nM)-induced resorption; 10 μM TAM was ineffective in blocking resorption, while 40-50 μM partially inhibited the response. TAM (100 μM) also completely blocked prostaglandin E2 (30 nM)- and 1,25-dihydroxy vitamin D3 (0.5 nM)-induced bone resorption. A 16-h pretreatment with TAM blocked subsequent stimulation of resorption by PTH, whereas 3.5- or 7-h pretreatment with antiestrogen was ineffective in blocking the response. Both protein and DNA syntheses were inhibited by continuous treatment (48 h) with the antiestrogens. When antiestrogen-pretreated (16 h) bones were transferred to fresh medium not containing antiestrogen, protein and DNA syntheses recovered to approximately half the control (nonantiestrogen-treated) values within 48 h. Bone resorption, however, was still completely inhibited even though macromolecular synthesis had substantially recovered. Thus, mechanisms other than macromolecular synthesis inhibition could be involved in the inhibition of bone resorption by the nonsteroidal antiestrogens TAM and CLO.

L47 ANSWER 25 OF 26 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 16

ACCESSION NUMBER: 1984:185270 BIOSIS
DOCUMENT NUMBER: PREV198477018254; BA77:18254
TITLE: ESTRADIOL AND TAMOXIFEN STIMULATION OF LAPINE ARTICULAR CHONDROCYTE PROSTAGLANDIN SYNTHESIS.
AUTHOR(S): ROSNER I A [Reprint author]; MALEMUD C J; HASSID A I;

GOLDBERG V M; BOJA B A; MOSKOWITZ R W
CORPORATE SOURCE: CARTILAGE RES LAB, DEP MED, CASE WESTERN RESERVE UNIV, CLEVELAND, OHIO 44106, USA
SOURCE: Prostaglandins, (**1983**) Vol. 26, No. 1, pp. 123-138.
CODEN: PRGLBA. ISSN: 0090-6980.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB The effect of estradiol and tamoxifen on prostaglandin (PG) synthesis by rabbit articular chondrocytes in secondary monolayer cultures was investigated. Radioimmunoassay for **PGE2**, **PGF2**. **alpha**., 6-oxo-PGF1α and thromboxane B2 was performed on media from cultures containing estradiol and **tamoxifen** (10-12-10-7 M). Radiometric TLC was also carried out. The time course of estradiol/tamoxifen effect on chondrocyte PG synthesis was evaluated and its relationship to cell density in culture examined. Estradiol stimulated the synthesis of PG by chondrocytes. Stimulation was noted at picomolar concentrations of estradiol without further stimulation at markedly higher concentrations. In time studies, after a lag, the effect of estradiol was present fully by 5 h, remained steady for 24 h and then declined by 48 h. Estradiol stimulation of PG synthesis was dependent upon chondrocyte culture plating density. Tamoxifen stimulated chondrocyte PG synthesis to relatively lower levels than estradiol. The characteristics of estradiol/tamoxifen stimulation of chondrocyte PG synthesis suggest a mechanism involving estradiol cytoplasmic receptors.

L47 ANSWER 26 OF 26 EMBASE
ACCESSION NUMBER: 77184042 EMBASE
DOCUMENT NUMBER: 1977184042
TITLE: Effects of prostaglandins and other drugs on the cyclic AMP content of cultured bone cells.
AUTHOR: Yu J.H.; Wells H.; Ryan Jr. W.J.; Lloyd W.S.
CORPORATE SOURCE: Oral Pharmacol. Lab., Boston Univ. Sch. Grad. Dent., Boston, Mass. 02118, United States
SOURCE: Prostaglandins, (**1976**) Vol. 12, No. 4, pp. 501-513.
CODEN: PRGLBA
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
005 General Pathology and Pathological Anatomy
023 Nuclear Medicine
LANGUAGE: English

AB Prostaglandins of the E series (PGE1 and PGE2) may be involved in disease related, localized loss of bone. E prostaglandins increase the cyclic AMP content of many cells; and, to determine whether their effects on bone are mediated by cyclic AMP, the effects of E prostaglandins and of other agents on the cyclic AMP content of cultured bone cells were examined. PGE2 produced a rapid, marked and dose related increase in the cyclic AMP content of confluent monolayers of bone cells isolated from newborn rat calvaria. At 2.8 x 10-6 M, PGE1 and PGE2 had approximately the same effect, while the effect of PGF(2α) was much less pronounced. In the presence of theophylline, PGE2 had a more marked effect than parathyroid hormone (PTH) and the combination of PGE2 and PTH had a synergistic effect. The divalent, cationic, ionophore, A23187, produced an increase in cellular cyclic AMP and had an additive effect in combination with PGE2. Synthetic salmon calcitonin (CT), which inhibits the bone resorptive effect of PGE2, increased cellular cyclic AMP and had

an additive effect in combination with PGE2. A prostaglandin antagonist, SC 19220, partially inhibited the resorptive effect of PGE2 and reduced its effect on cellular cyclic AMP. The calcium antagonist, D600, inhibited the bone resorptive effects of PGE2 but had no effect on increased cellular cyclic AMP produced by PGE2. The marked effect of PGE2 on bone cell cyclic AMP suggests that this action is involved in the mechanism of **PGE2** related **bone loss**. The fact that agents with different effects on PGE2 induced increases in cellular cyclic AMP can inhibit its resorptive actions, suggests that PGE2 induced changes in cyclic AMP may be related less to its resorptive actions than to its inhibitory effect on bone formation.

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                 84449-90-1 OR  10540-29-1 OR 68047-06-3)/RN
L2             7 SEA FILE=REGISTRY ABB=ON  (180915-84-8 OR 180915-78-0 OR
                 180916-16-9 OR 193274-89-4 OR 180916-14-7 OR 180915-86-0 OR
                 180916-15-8)/RN
L3             4 SEA FILE=REGISTRY ABB=ON  (PGD1 OR PGD2 OR PGE2 OR PGE1 OR
                 PGF2 OR PGF2A)/CN
L4             1 SEA FILE=REGISTRY ABB=ON  PGF2A/CN
L5             5 SEA FILE=REGISTRY ABB=ON  L3 OR L4
L6             6 SEA FILE=REGISTRY ABB=ON  L5 OR 195962-24-4/RN
L7         10946 SEA FILE=HCAPLUS ABB=ON  L1 OR ?DROLOXIFENE? OR ?RALOXIFENE?
                 OR ?TAMOXIFEN?
L10           15 SEA FILE=HCAPLUS ABB=ON  L7(20A)(L3 OR L6 OR PGD1 OR PGD2 OR
                 PGE2 OR PGE1 OR PGF2 OR PGF2A OR PGF2A)
L11            3 SEA FILE=HCAPLUS ABB=ON  L10 AND (?BONE?(W)(?LOSS? OR ?RESORP?
                 OR ?LOSE?) OR ?OSTEOPOROS? OR ?PAGET?)
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                 OR ?TAMOXIFEN?
L20            6 SEA FILE=HCAPLUS ABB=ON  L12 AND (PRD<19960228 OR PD<19960228)
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L28          239 SEA FILE=HCAPLUS ABB=ON  L15(3A)(?BONE?(W)(?LOSS? OR ?RESORP?
                 OR ?LOSE?) OR ?OSTEOPOROS? OR ?PAGET?)
L29           37 SEA FILE=HCAPLUS ABB=ON  L28 AND (PRD<19960228 OR PD<19960228)
L36           14 SEA FILE=HCAPLUS ABB=ON  L23(2W)(?BONE?(W)?LOSS? OR ?OSTEOPOROS
                 ? OR ?PAGET?)
L44            9 SEA FILE=HCAPLUS ABB=ON  L36 AND (PRD<19960228 OR PD<19960228)
L48            8 SEA FILE=USPATFULL ABB=ON  L20 OR L29 OR L44

=> d ibib abs l48 1-8

L48  ANSWER 1 OF 8  USPATFULL on STN
ACCESSION NUMBER:        2000:161019  USPATFULL
TITLE:                   Estrogen agonists/antagonists
INVENTOR(S):             Cameron, Kimberly O., East Lyme, CT, United States
                         Dasilva-Jardine, Paul A., Providence, RI, United States
                         Ke, Hua Zhu, Ledyard, CT, United States
                         Rosati, Robert L., Stonington, CT, United States
PATENT ASSIGNEE(S):      Pfizer, Inc., New York, NY, United States (U.S.
                         corporation)

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 6153622               20001128
APPLICATION INFO.:       US 1998-141613           19980828  (9)
RELATED APPLN. INFO.:    Continuation-in-part of Ser. No. US 849726

                               NUMBER         DATE
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PRIORITY INFORMATION:    WO 1995-IB286      19950424                <--
DOCUMENT TYPE:           Utility
FILE SEGMENT:            Granted
PRIMARY EXAMINER:        Davis, Zinna Northington
LEGAL REPRESENTATIVE:    Richardson, Peter C., Benson, Gregg C., Brokke, Mervin
                         E.
NUMBER OF CLAIMS:        25
EXEMPLARY CLAIM:         1
```

LINE COUNT: 1615
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds of this formula ##STR1## are useful for treating or preventing, obesity, breast cancer, osteoporosis, endometriosis, cardiovascular disease and prostatic disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L48 ANSWER 2 OF 8 USPATFULL on STN
ACCESSION NUMBER: 96:16977 USPATFULL
TITLE: Selective regulation of B lymphocyte precursors by hormones
INVENTOR(S): Kincade, Paul W., Oklahoma City, OK, United States
Medina, Kay, Moore, OK, United States
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, Oklahoma City, OK, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5494899		19960227	<--
APPLICATION INFO.:	US 1994-224236		19940407	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-44280, filed on 7 Apr 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wityshyn, Michael G.
ASSISTANT EXAMINER: Degen, Nancy J.
LEGAL REPRESENTATIVE: Arnall Golden & Gregory
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 987
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB It has been determined that estrogen and other hormones elevated in pregnancy induce a specific modulation of lymphocyte precursor cell production. The immune system of an animal or bone marrow cells in culture can therefore be modulated in a specific manner by administration of hormones elevated during pregnancy, such as estrogen and estrogen-like compounds or compounds that interfere with the synthesis or activity of these hormones, to increase or decrease production of B lymphocyte precursor cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L48 ANSWER 3 OF 8 USPATFULL on STN
ACCESSION NUMBER: 95:90541 USPATFULL
TITLE: Method for inhibiting bone loss using 6-hydroxy-2-(4-hydroxyphenyl)-benzo[B][2-(piperidin-1-yl)ethoxyphenylimethanone hydrochloride
INVENTOR(S): Black, Larry J., Indianapolis, IN, United States
Cullinan, George J., Trafalgar, IN, United States
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5457117		19951010	<--
APPLICATION INFO.:	US 1994-329396		19941026	(8)

DISCLAIMER DATE: 20120228
RELATED APPLN. INFO.: Division of Ser. No. US 1994-180522, filed on 12 Jan

1994, now patented, Pat. No. US 5393763 which is a continuation of Ser. No. US 1992-920933, filed on 28 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Sales, James J., Dahling, Gerald V.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 944
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The current invention provides a method useful for inhibiting the loss of bone using 6-hydroxy-2-(4-hydroxyphenyl)-benzo(B)thien-3-yl-4[2-(piperidin-1-ethoxyphenol]methanone hydrochloride.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L48 ANSWER 4 OF 8 USPATFULL on STN
ACCESSION NUMBER: 95:18433 USPATFULL
TITLE: Methods for inhibiting bone loss
INVENTOR(S): Black, Larry J., Indianapolis, IN, United States
Cullinan, George J., Trafalgar, IN, United States
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5393763		19950228	<--
APPLICATION INFO.:	US 1994-180522		19940112	(8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-920933, filed on 28 Jul 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Henley, III, Raymond J.
ASSISTANT EXAMINER: Criares, T. J.
LEGAL REPRESENTATIVE: Sales, James J., Dahling, Gerald V., Cantrell, Paul R.
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
LINE COUNT: 1037
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The current invention provides methods and pharmaceutical formulations that are useful for inhibiting the loss of bone. These methods and formulations can be used without the associated adverse effects of estrogen therapy, and thus serve as an effective and acceptable treatment for osteoporosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L48 ANSWER 5 OF 8 USPATFULL on STN
ACCESSION NUMBER: 93:87380 USPATFULL
TITLE: Remedies for bone diseases
INVENTOR(S): Niikura, Kazuaki, Ibaraki, Japan
Nakajima, Yoshimitsu, Ibaraki, Japan
Notsu, Yoshitada, Ibaraki, Japan
Ono, Ryuji, Ibaraki, Japan
Nakayama, Osamu, Ibaraki, Japan
PATENT ASSIGNEE(S): Klinge Pharma GmbH, Munich, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 5254594	19931019	<--
APPLICATION INFO.:	US 1992-865106	19920408 (7)	

	NUMBER	DATE	
PRIORITY INFORMATION:	JP 1991-166944	19910409	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Waddell, Frederick E.
ASSISTANT EXAMINER: Moezie, Minna
LEGAL REPRESENTATIVE: Brumbaugh Graves Donohue & Raymond
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 142
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Remedies for bone diseases comprising, as active ingredient, droloxifene or a salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L48 ANSWER 6 OF 8 USPATFULL on STN
ACCESSION NUMBER: 92:44810 USPATFULL
TITLE: Bone growth factors and inhibitors of bone resorption for promoting bone formation
INVENTOR(S): Adams, Steven W., Sunnyvale, CA, United States
Armstrong, Rosa, Palo Alto, CA, United States
Rosen, David, San Jose, CA, United States
PATENT ASSIGNEE(S): Celtrix Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5118667		19920602	<--
APPLICATION INFO.:	US 1991-695310		19910503 (7)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schain, Howard E.
ASSISTANT EXAMINER: Koh, Choon
LEGAL REPRESENTATIVE: Morrison & Foerster
NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 679
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Bone growth factors are used to stimulate new bone formation when administered with agents that inhibit bone resorption. These therapeutic combinations result in an enhanced rate of bone formation with an increase in bone mass.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L48 ANSWER 7 OF 8 USPATFULL on STN
ACCESSION NUMBER: 90:87369 USPATFULL
TITLE: Use of clomiphene to increase bone mass in premenopausal women
INVENTOR(S): Jensen, Pamela S., Camden, ME, United States
Comite, Florence, New Haven, CT, United States
PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4970237		19901113	<--
APPLICATION INFO.:	US 1989-311018		19890214	(7)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1987-28371, filed on 20 Mar 1987
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lipovsky, Joseph A.
LEGAL REPRESENTATIVE: Sprung, Horn, Kramer & Woods
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 597
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the use of clomiphene in preventing osteoporosis in humans and treating human patients experiencing osteoporosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L48 ANSWER 8 OF 8 USPATFULL on STN
ACCESSION NUMBER: 89:27938 USPATFULL
TITLE: Use of clomiphene to predict fertility in a human female
INVENTOR(S): Jensen, Pamela S., Camden, ME, United States
Comite, Florence, New Haven, CT, United States
PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4820736		19890411	<--
APPLICATION INFO.:	US 1987-28371		19870320	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Meyers, Albert T.
ASSISTANT EXAMINER: Krosnick, Freda L.
LEGAL REPRESENTATIVE: Sprung Horn Kramer & Woods
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 554
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of clomiphene and its citrate salt in predicting fertility in a human female.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

These are the 6 cits with both sets of compds.


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=> d an ti 1-6

L10  ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1997:171204  HCAPLUS
DN   126:210851
TI   Altered uterine sensitivity to oxytocin and prostaglandin F2α in
     dimethylbenz(a)anthracene (DMBA)-induced rat mammary carcinoma: the
     effects of tamoxifen and/or recombinant human interferon α2b therapy

L10  ANSWER 2 OF 6  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1995:445248  HCAPLUS
DN   122:205484
TI   Effects of estradiol and tamoxifen on oxytocin-induced phospholipase C
     activation in human myometrial cells

L10  ANSWER 3 OF 6  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1993:509317  HCAPLUS
DN   119:109317
TI   Effects of onapristone, tamoxifen and ICI 182780 on uterine prostaglandin
     production and luteal function in nonpregnant guinea pigs

L10  ANSWER 4 OF 6  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1989:433304  HCAPLUS
DN   111:33304
TI   Effects of antirheumatic drugs on the interleukin 1α-induced
     synthesis and activation of proteinases in articular cartilage explants in
     culture

L10  ANSWER 5 OF 6  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1986:219385  HCAPLUS
DN   104:219385
TI   Hormonal effects of PGF2α output by cultures of epithelial and
     stromal cells in human endometrium

L10  ANSWER 6 OF 6  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1986:62348  HCAPLUS
DN   104:62348
TI   In vitro inhibition with antiestrogens of estradiol effects on
     prostaglandin F2α production by human endometrium and endometrial
     epithelial cells
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                 84449-90-1 OR  10540-29-1 OR 68047-06-3)/RN
L2             7 SEA FILE=REGISTRY ABB=ON  (180915-84-8 OR 180915-78-0 OR
                 180916-16-9 OR 193274-89-4 OR 180916-14-7 OR 180915-86-0 OR
                 180916-15-8)/RN
L3             4 SEA FILE=REGISTRY ABB=ON  (PGD1 OR PGD2 OR PGE2 OR PGE1 OR
                 PGF2 OR PGF2A)/CN
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L5             5 SEA FILE=REGISTRY ABB=ON  L3 OR L4
L6             6 SEA FILE=REGISTRY ABB=ON  L5 OR 195962-24-4/RN
L7         10946 SEA FILE=HCAPLUS ABB=ON  L1 OR ?DROLOXIFENE? OR ?RALOXIFENE?
                 OR ?TAMOXIFEN?
L10           15 SEA FILE=HCAPLUS ABB=ON  L7(20A)(L3 OR L6 OR PGD1 OR PGD2 OR
                 PGE2 OR PGE1 OR PGF2 OR PGF2A OR PGF2A)
L11            3 SEA FILE=HCAPLUS ABB=ON  L10 AND (?BONE?(W)(?LOSS? OR ?RESORP?
                 OR ?LOSE?) OR ?OSTEOPOROS? OR ?PAGET?)
L12           15 SEA FILE=HCAPLUS ABB=ON  L10 OR L11
L14           11 SEA FILE=REGISTRY ABB=ON  L1 OR L2
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